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A GLOMERULAR DOMINANCE IN BRIGHT'S DISEASE.*

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To Richard Bright in 1827 and in subsequent publications the disease that we now know by his name was very simple. His clinical conception was unified about one characteristic, boiling the urine caused a precipitation; this meant disease of the kidney; albuminuria was evidence of a pathological state of the kidney. Bright recognized that with albuminuria went varying manifestations of abnormal function, not of the kidney alone, but of the body in general; on postmortem examination he saw that the kidneys from these patients varied greatly in appearance, but there was unity in the fact that none of the kidneys were normal. To Richard Bright albuminuria was the dominant characteristic of kidney disease during life, and on postmortem examination disease of the kidney was for Richard Bright the dominant characteristic. Whatever variety there might be in the clinical picture, and Bright recognized and described many of them, the common feature was albuminuria; whatever variety there might be in the pathology of the kidney and other organs, and Bright described and pictured most of these as we recognize them today, the common feature was that the kidneys were diseased. To Richard Bright the concept of kidney disease was simple; neither in 1827 nor in 1836 did he use the term, nephritis. Had he done so, very probably he would have used the terms, nosos nephritis, in the original Greek usage "disease

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in, about or concerning the kidney", that being the significance in classical Greek of the ending "-itis" after the name of an organ or tissue as indicated by Thucydides having Nicias say "nosos nephritis", while Hippocrates in one place uses the words "phthisis nephritis". It was only at a later date that the ending "-itis" came to have the medical connotation of "inflammation of", and this departure from the original usage has put us in a dilemma of terminology that long has been a bug-bear to classificationists of kidney disease.

The pathologists early found that under the microscope there was fully as much, if not even more, variation in the findings in different patients, who during life had shown albuminuria as evidence of disease of the kidney, than was apparent in the different gross appearances of the kidney as seen and pictured by Richard Bright. For a time pathologists maintained a unity of concept in that they considered these variations in both macroscopic and microscopic appearance of the kidneys no more than an expression of the patients having died at different stages of a single type of kidney process. This was the view in the time of Frerichs, 1851, and continued to be accepted by some until Weigert, in 1879, crystallized the idea that had been steadily growing in favor in England and Germany, that not one, but several, disease processes were present in nephritis or Bright's disease, the concept which now prevails among both pathologists and clinicians.

This latter point of view has been responsible fundamentally for complex classifications of Bright's disease. This complexity has increased as the microscope and clinical methods have shown more and more variation in individual patients to be used as a basis of grouping them in accordance with their resemblances and differences into more and more groups, each regarded as possessing some important individual characteristics, until classifications, whether of the pathologist or of the clinician, have grown into the great complexity, such as now very generally prevails.

A long time interest in Bright's disease, both in its pathological and clinical manifestations, has made me wonder whether such complexity of classification is necessary to a satisfactory understanding of the disease, and whether there may not be more to gain in an understanding of what happens when the kidney becomes diseased, by considering more the common factors and functions among the disturbances and less the differences that multiply the subdivisions of our classifications.

It is true that the normal kidney is very complex both in structure and function, and yet, after all, it is only an aggregate of units, supported in a framework of tissue functioning only to hold these units together and to protect them from external injury. This unit centers itself very naturally in one structure, the glomerulus, into which comes a blood flow and out of which passes a blood flow and a canal lined by cells with a definite function. Here is a unit

of concept in renal function, normal and abnormal, the glomerulus. Is it possible to build on such a unitary concept a simpler understanding of the diseases of the kidney?

The glomerulus is a vascular unit, an aggregation of branching and converging capillaries, covered by a layer of greatly thinned, tubular epithelium connected with a tubule lined at different levels by various types of cells. The total surface of the capillary tuft in the glomerulus is great, and in their aggregate an enormous area of capillary surface exists in this way. Through the glomeruli daily passes a vast amount of blood, aërated and loaded with many substances collected from all parts of the body. Between this circulating blood within the glomerular tuft and the external world, communicated with through the tubule, ureter, bladder and urethra, exists but a thin membrane of dual composition, capillary wall and renal epithelium. The situation is, in a way, analogous to that in the lung, where capillaries are spread out in the walls of the pulmonary alveoli, so that in the lung between the circulating blood and the external world is but a thin membrane made up of capillary wall and pulmonary epithelium. In each, endothelial and epithelial structures are in close apposition to form a colloidal membrane, but these two membranes, so alike in structure, function in vastly different ways; in the kidney, the normal membrane allows the passage of water and certain small molecule solutes; in the lung, the normal membrane allows the two-way passage of two gases, oxygen and carbon dioxide; each of these membranes holds back what the other normally allows to pass; this illustrates how differently structures, which under the microscope look alike, may function and emphasizes the probability that structures may undergo changes, that profoundly alter their function, without our being able to see any structural change in them under the microscope.

The afferent blood supply to the glomerulus serves to bring to the glomerulus blood for it to lose certain constituents, which pass through the glomerular membrane into the tubule. The efferent blood supply carries this blood to the tubule, where through the epithelium of the tubules and its basal membrane further changes in the blood are made, largely additive in nature. The tubule serves to carry off the water and its solutes that pass through the glomerular membrane but in this passage modify this fluid, largely by a subtractive process, before it is discharged into the external world as urine. What happens in this way constitutes the function of the kidney, a function dominated by the glomerulus of each unit, a function that is in essentials a physico-chemical process, in which the glomerular membrane plays the dominant part. For this mechanism to function normally there is necessary a free blood flow through the glomerulus and a normal glomerular membrane; these are dominantly important. Of subsidiary importance is a normal epithelial lining to the tubule running from the glomerulus.

If the glomerulus dominates the kidney in its normal function, as just described, so the glomerulus dominates the abnormal function that occurs in Bright's disease or, in other words, there is a glomerular dominance in Bright's disease. Let me explore this idea further. As already stated, for normal renal function there is necessary to each unit of structure a free blood flow to the glomerulus and a normal glomerular membrane discharging into a normal tubule; in this, glomerulus is dominant and tubule subsidiary in function. With these functioning normally in a normal body we have urine, proportionate in amount and specific gravity to intake of fluid and free of albumin, casts and cells, a blood stream with its constituents balanced within relatively slightly fluctuating figures and a blood pressure within normal limits. In Bright's disease some or all of these in varying proportions depart from their norms, and these departures along with secondary effects on body organs and tissues make up the clinical picture of the various forms of Bright's disease.

In Bright's disease the glomerular membrane either leaks or holds back constituents of the blood stream, and the blood flow through the glomerulus remains normal or is throttled down to a lessened flow; the throttling may take place inside or outside of the glomerulus. Acceleration of blood flow through the glomerulus occurs; as far as Bright's disease is concerned, this seems to be only a compensatory action and merely helps to lessen the effect of retarded function in other glomeruli. Finer glomerular leakage permits molecules larger than normal to pass, such as albumin, globulin and fibrinogen, and holds back cells; coarser glomerular leakage permits in addition the passage of cells, red blood cells and white blood cells. A thickened glomerular membrane plays a part in retention of substances otherwise excreted from the blood stream, but retention chiefly is a function of throttled blood flow, whether the throttling is outside the glomerulus or due to narrowing of the capillary lumen inside the glomerulus. Retention also is related to the atrophy and disappearance of glomeruli, which occurs in Bright's disease.

In Bright's disease there are lesions in the tubules, but these changes are relatively unimportant in most cases so far as the clinical picture and renal function are concerned. Their part definitely, so far as we know at present, is a subsidiary one.

If the glomerular changes dominate in Bright's disease, as seems to be the case, then we can unify our concept of Bright's disease, building around glomerular function. The sequences of pathological changes in the glomeruli largely can be simplified to those causing glomerular leakage and those causing glomerular throttling in varying combinations of severity.

If the glomeruli leak, we have albuminuria with cylindruria or hematuria; leukocytes, too, appear, but rarely are they very numerous in the urine of simple Bright's disease. If leakage of albumin continues so that plasma protein becomes low, we have chronic

renal edema of the body. If the glomerulus only leaks, there is no abnormal retentions in the blood stream and no elevation of blood pressure. If the glomeruli are throttled, we have abnormal retentions in the blood stream and elevation of blood pressure. If there are abnormal retentions in the blood stream, and this chiefly is non-protein nitrogen retention, anemia and uremic symptoms develop. If the blood pressure is elevated and continues high, we have secondary cardiovascular changes. If these are sufficient to cause cardiac decompensation, circulatory edema will appear. These several changes develop in different patients with Bright's disease in different proportions; from this is derived the varying symptomatology and physical findings in what we call Bright's disease.

As far as throttling of the glomerular blood flow is concerned, the effect is the same whether the throttling is in the capillaries of the glomerulus, in the afferent or even efferent arteriole of the glomerulus or in the larger renal vessels anywhere in their course between the aorta and the afferent arteriole of the glomerulus; not the situation of the throttling, but its degree, is what determines the effect on function. This is well shown by the experimental work of D. R. Drury, published in April, 1932, who, placing a not-binding ligature about the renal artery of young animals, got his throttling effect from the artery gradually becoming constricted, by the pressure of a ligature that had not stretched as the artery grew larger with growth of the animal, this producing renal atrophy with polyuria and nitrogen retention; and of Goldblatt, in which the throttling of the glomeruli was brought about by a constricting band applied about the main renal artery of adult animals, resulting in a steady rise in blood pressure without or with disturbance of renal function, depending upon the degree of constriction of the main renal artery, work first reported by Goldblatt on November 11, 1932, before the Academy of Medicine of Cleveland and subsequently published in 1934. It is of further interest that in 1909 William S. Halsted published a paper entitled "Partial, Progressive and Complete Occlusion of the Aorta and Other Large Arteries in the Dog by Means of the Metal Band" in which he has an illustration of the kidneys, on the artery to one of which had been placed a compressing metal band; that kidney is atrophied to about one-quarter the size of the one on whose artery no band had been placed.

In the preceding paragraphs I have attempted to build up a concept of Bright's disease unified about the glomerulus, a glomerular dominance in the process. To bring about the clinical picture and physical findings of Bright's disease two changes in the glomeruli are of dominant import, glomerular leakage and glomerular throttling. If you will accept these ideas, let me elaborate them in relation to the classification and the symptomatology, including physical findings, of Bright's disease, showing how from these glomerular

changes, leakage and throttling, can come about the chief clinical findings that we encounter in Bright's disease.

First, as to classification, for a long time I have taught to my students a very simple clinical classification of Bright's disease as follows:

Acute and Subacute Bright's Disease (Hemorrhagic, Edematous).
Chronic Bright's Disease With Renal Edema.
Chronic Bright's Disease Without Renal Edema.

In these groups glomerular leakage dominates in all except the last; in the last glomerular throttling dominates. With dominant glomerular throttling there is practically always an accompanying, but less important, glomerular leakage; with dominant glomerular leakage there may be periods of glomerular throttling. In certain patients the two processes seem of almost equal importance; these may be called Mixed Types of Chronic Bright's Disease.

What I have given is a clinical classification. At different stages there is a corresponding pathological picture. For example, the first three chief groups would be called by the pathologist glomerulonephritis, acute, subacute and chronic; in them, glomerular leakage has been the chief disturbance of function; the finer histological changes in the glomeruli probably would be quite different from case to case at any of the three stages, acute, subacute and chronic, depending on what part or parts of the glomerular structure was involved, on how great a degree of involvement there was and on how long the process had been going on, whether the leakage is chiefly of albumin or of blood cells. These changes would range from those so slight as to be detected only with special staining technique, which occur when there is a very extensive leakage of albumin as in the edematous type of acute Bright's disease (nephrosis syndrome) to those marked enough to make the glomeruli visible to the unaided eye as in some cases of subacute and chronic Bright's disease. Sometimes, but not always, these different pathological appearances can be recognized by the clinical course of the disease; to attempt to do so in individual cases would bring too great uncertainty to justify the introduction into the clinical classification of numerous subdivisions to tally with these pathological variations.

In contrast to these three, the last group, Chronic Bright's Disease Without Renal Edema, with a definite distinctive clinical picture is made up of cases that pathologically show great variation. The reason for this is that throttling of the glomeruli dominates and that is the chief cause of the most important clinical characteristics of the group, namely hypertension, nitrogen retention and anemia. The result is much the same whether the throttling occurs inside the glomerulus, just outside in the glomerular arteriole or more distantly in the course of the renal artery and its branches. This throttling can be the end result of 4 different types of pathological change in the kidney: 1, glomerulonephritis; 2, vascular nephritis,

sometimes called malignant hypertension; 3, pyelonephritis; 4, rarely, so-called nephrosis. Nephrosis in my opinion, is a form of glomerulonephritis, in which glomerular leakage of albumin is the outstanding clinical manifestation.

You can follow in certain instances a patient that progressively will pass through stages showing the clinical features of all four main groups in the above clinical classification, that is acute, subacute and chronic Bright's disease with renal edema and finally, chronic Bright's disease without renal edema; this not infrequently happens. In the beginning glomerular leakage dominates; at the end glomerular throttling dominates; in between, both processes go on in varying proportion. As throttling of the glomerulus becomes prominent, leakage lessens; hence with a marked early albuminuria blood pressure is normal, and there is no nitrogen retention and no anemia; later as albuminuria lessens, blood pressure rises, nitrogen retention begins and later, anemia follows. As these changes go on, glomeruli, at first larger than normal, shrink, tubules atrophy and interstitial tissue increases; the early large kidney of acute and subacute glomerulonephritis becomes the secondarily contracted kidney of chronic glomerulonephritis. Other patients commencing as acute hemorrhagic Bright's disease eventually will reach this same end stage, unless they die at an earlier stage or recover from the acute stage.

By no means is it possible in all cases to trace clinically these several stages. Some cases recover in the acute stage, and there is no subsequent progression. There may be a long latent period of apparent health between the early acute and the late chronic atrophic stage; the acute stage may have shown no symptoms; possibly from the onset the process has been insidious, free of symptoms and so clinically latent, until glomerular throttling begins; prior to this, the stage of glomerular leakage has been so mild as to pass unnoted.

In just this same way essential vascular hypertension eventually leads to glomerular throttling; when it does, the clinical picture is the same as that of the late stage of glomerulonephritis as just described. This change may be slow or rapid in its progressive development, and this causes different clinical pictures. When rapid, some like to use the term, malignant hypertension. To me it has seemed less confusing, if the term malignant hypertension is not used, since I consider it but a variant of vascular nephritis and not a distinctive pathological change. Sometimes evidence of vascular lesion with hypertension appears only at the time that glomerular throttling is causing its usual characteristic renal symptoms; at other times, it long antedates evidence of disturbed renal function, and we have almost only hypertension as an evidence of glomerular throttling. Pathologically this is vascular nephritis.

Similarly, pyelonephritis may develop into a chronic or even healed stage, so far as the infection is concerned, but one in which

kidney atrophy with glomerular throttling develops to end in a clinical syndrome having the chief characteristics just described for the late stages of chronic glomerulonephritis or of vascular nephritis, namely, hypertension, renal retention and anemia. Pathologically, both glomerular lesions and vascular lesions in combination contribute to this end result in which atrophy and connective tissue increase are prominent.

Particularly interesting in this respect is a rare case of so-called nephrosis, which ends in a stage of high blood pressure, nitrogen retention and anemia. The change that takes place is almost a pure demonstration of what I have been discussing, namely glomerular dominance, at first with pure leakage and later with throttling. The glomerular lesion of so-called nephrosis is very simple; the glomerular membrane is changed, so that it no longer holds back albumin and globulin, but few or no cells go through. The only histological evidence of this is a slight hyaline appearance and a very slight thickening of the capillary wall and opposed epithelial membrane; special staining technique is required to demonstrate these slight changes. If the condition retains its nephrosis characteristics, as time goes on, the only change is more thickening of the glomerular loops but without cellular proliferation; only glomerular leakage goes on. In a very rare instance, however, the thickening of the wall gets marked enough to lead to some obstruction of blood flow in the capillary loops, *i. e.*, throttling of the glomerulus; now blood pressure rises and nitrogen retention begins; the late stage here is just as described for the preceding three forms; throttling of the glomerulus eventually has dominated the picture. George Fahr has described such cases; I have never observed one.

In acute nephritis, in which glomerular leakage dominates, occasionally temporary throttling of the glomeruli appears, and in these cases of acute nephritis hypertension and nitrogen retention appear for a short period, later to disappear.

Throughout this discussion I have used the term renal edema to mean that form of edema resulting from low plasma protein, especially low plasma albumin; it has no relation to circulatory insufficiency. With glomerular throttling we have hypertension; if hypertension is marked enough and persistent enough, cardiac hypertrophy results, and this often leads to cardiac insufficiency and the edema of congestive heart failure, or circulatory edema. These two types of edema should be distinguished in an understanding of Bright's disease.

With patients of this last group, Chronic Bright's Disease Without Renal Edema, seen only in the late stages, it may not be possible to say what type of lesion of the kidney is responsible for the condition. When there has been opportunity to follow the clinical developments over a period of time, as a rule, some one of these four separate ways of progression into the end stage can be recognized

as having led up to the end stage of Chronic Bright's Disease Without Renal Edema, and we are able to say that glomerular throttling has resulted from progressing glomerulonephritis, vascular nephritis, pyelonephritis or the nephrosis syndrome.

Summary. In the preceding discussion I have attempted to elaborate a concept of Bright's disease in which the explanation of its major clinical symptoms and signs can be found in disturbances in the integrity of the function of the glomeruli of the kidney. These disturbances in glomerular function are: 1, abnormal leakage of blood constituents into the tubules of the kidney; and, 2, throttling of the blood flow through glomerular capillaries. These occur in varying combination of intensity from the one in which leakage is almost the sole abnormality to the one in which throttling of blood flow is the chief departure from normal with all sorts of combinations of these two disturbances in different individual patients. The most distressing clinical result of leakage is renal edema and of throttling is hypertension and nitrogenous retention. It is this that I have meant by "A Glomerular Dominance in Bright's Disease."

HEMOLYSINS AS THE CAUSE OF CLINICAL AND EXPERIMENTAL HEMOLYTIC ANEMIAS.

With Particular Reference to the Nature of Spherocytosis and Increased Fragility.*†

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In 3 successive cases of acute non-familial hemolytic anemia, active serum isohemolysins were discovered which were capable of hemolyzing red cells of their own type and of Group 0.[16] These isohemolysins presented all the classical criteria of immune bodies: inactivation by heat, reactivation by the addition of complement, slightly increased activity after storage in the ice-box for several hours, somewhat diminished activity after prolonged storage in the ice-box, and a positive Ehrlich-Morgenroth phenomenon. In addi-

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tion, inactivation could be effected by incubation of the serum with normal serum. In the first 2 cases, which were subacute in type, the blood picture was "pseudomacrocytic," careful analysis indicating that most of the large red blood cells were reticulocytes and not orthochromatic macrocytes. These cases were completely refractory to blood transfusions, but dramatic recoveries took place when splenectomy was performed. In the third case, the blood picture was microcytic, being characterized before splenectomy by the presence of marked spherocytosis and greatly increased fragility of the red cells in hypotonic salt solutions. With improvement of the patient after splenectomy, spherocytosis gradually diminished and finally disappeared, the erythrocyte fragility became normal, and the hemolysins could no longer be demonstrated.

As these cases were studied, several possibilities suggested themselves: 1, that acute hemolytic anemia and possibly other hemolytic syndromes might be due to the action of hemolysins; 2, that the differences in the type of hemolytic reaction might be a matter of degree and dependent upon the "dosage" of hemolysin; and 3, that spherocytosis and increased fragility might be due to the action of hemolysin rather than dependent upon a disturbed formation of red cells in the bone marrow. In order to test these possibilities, it was decided to reproduce hemolytic anemia experimentally by the use of a hemolytic serum immunologically similar to that found in our clinical cases. The production of immune hemolysins by the injection of the red cells of one animal species into the blood stream of another has been practised almost since the beginning of immunologic studies. By this means a heterophilic hemolytic serum is produced which, when injected into the donor animal species, will result in the production of hemolysis. Because the guinea pig is readily available for hematologic studies and its red cells are so similar in nature to those of man, it was chosen for the donor species. The rabbit was used for the production of an anti-guinea pig hemolytic serum. Although the production of hemolytic anemia by this method has been accomplished by other investigators in the past, exact hematologic studies and their correlation with clinical syndromes have not hitherto been fully carried out. The results of of these studies are the subject of the present paper.

Methods and Material. 1. *Preparation of Hemolytic Sera.* Adult guinea-pigs weighing about 500 gm. were used. They were fed on a mixed diet of hay, seed, lettuce, carrots, and so on. Heart blood was obtained by puncture of the ether-anesthetized animal and washed with normal salt solution. The blood was then injected into the ear veins of rabbits in accordance with the following scale of dosage: 1st day, 0.5 cc.; 3d day, 1.0 cc.; 5th day, 1.0 cc.; 7th day, 1.0 cc.; 11th day, 1.5 cc. On the 19th day a trial bleeding was performed, and the rabbit serum titrated for anti-guinea pig hemolytic activity *in vitro*. The hemolytic titer at this time usually varied between 1 to 50 and 1 to 100, the agglutinin titer between 1 to 200 and 1 to 400. If the serum was sufficiently potent, it was inac-

tivated by heating to 56° C., for ½ hour, and phenol 0.4% was added as a preservative. All hemolytic serum was diluted to a final titration value of 1 to 50 (normal rabbit serum has a guinea pig hemolytic activity of under 1 to 10). Sera of high titer, up to 1 to 1600, have been prepared by the use of more frequent injections and by continuing injection over a longer period of time. The hemolytic sera thus prepared presented all the criteria of an immune serum which have been listed above. As with the human hemolytic serum, hemolytic activity could be inactivated by incubation with normal guinea-pig serum.

2. *Titration of Hemolysin.* The hemolytic sera were diluted 1 to 2, 1 to 4, 1 to 8, 1 to 16, 1 to 32, and so on. To 0.5 cc. of serum were added 0.5 cc. of a 2% suspension of washed guinea-pig red cells, 1.5 cc. of isotonic (0.85%) NaCl solution, and 0.5 cc. of a 10% fresh guinea-pig serum for complement. These materials were mixed and incubated at 37° for an hour before readings were made. The hemolytic titer was given by the last tube in which hemolysis was visible, the agglutinin titer by the last tube in which agglutination was visible.

3. *The Production and Study of the Hemolytic Syndromes.* Guinea-pigs were injected intraperitoneally and intramuscularly with varying doses of standardized (1 to 50) hemolytic serum, comparative studies with both methods of injection being made. Control injections with normal rabbit serum were also performed. Hematologic studies were made frequently, usually at daily intervals. Blood was obtained in small drops from one of the ear vessels. Hemoglobin estimations were made by the Newcomer method, so calibrated that 100% equaled 15.5 gm. of hemoglobin. Red blood cell and white blood cell counts were made with U. S. Bureau of Standards certified pipettes and hemacytometers. Platelet counts were performed according to the method of Dameshek.[15] Reticulocyte counts were performed in the ordinary "dry" manner on cover slips, brilliant cresyl blue and Wright's stain being used. Price-Jones curves[42b] were performed by counting 200 red cells, using a calibrated Leitz micrometer eyepiece. Hematocrit estimations were made by using Heller and Paul's dry oxalate mixture[30] for collection of the blood and the Wintrobe[49] hematocrit tubes. Estimations of the mean red cell thickness were made from the mean corpuscular volume and red cell diameter according to the following formula:

$$\text{Thickness} = \frac{\text{volume}}{\text{surface area}} = \frac{\text{mean corpuscular volume}}{\pi\ (\text{radius})^2}$$

In the determinations of hematocrit and fragility, separate sets of guinea-pigs were usually used because of the necessity of removing 2 cc. of heart blood at 1 to 3-day intervals. Fragility tests were performed according to the method of Daland and Worthley,[13] so modified that only a 10% suspension of red blood cells was used.

Postmortem examinations were performed in every instance. Smears from the bone-marrow were stained with Wright-Giemsa stain; sections of the bone-marrow and spleen were fixed in Zenker's solution, paraffin sections being prepared and stained with eosin-methylene blue.

Results. 1. *The Effect of Normal Rabbit Serum.* When normal rabbit serum was injected into guinea pigs (Chart 1), the effect was entirely negative except for minor fluctuations in erythrocyte counts and for slight reticulocytosis.

2. *The Comparative Effect of Intraperitoneal and Intramuscular Injections.* Identical small, medium and large doses of hemolytic serum were given intramuscularly or intraperitoneally to three sets

of 6 guinea pigs and their effects compared. In general, the effects were identical, the only difference being in the rapidity of the development of the hemolytic syndrome. Serum given intraperitoneally produced anemia more quickly, and with large doses resulted more quickly in death of the animal than when the injections were given intramuscularly. As judged from the survival times of the animals, the intraperitoneal route was 1.5 to 2 times as effective as the intramuscular. Intravenous administration was not attempted.

3. *The Comparative Effects of Various Dosages of Hemolytic Serum.* Varying dosages of hemolytic serum were given to 56 guinea pigs. The type of hemolytic effect produced varied directly with the amount of serum injected (Chart 2).

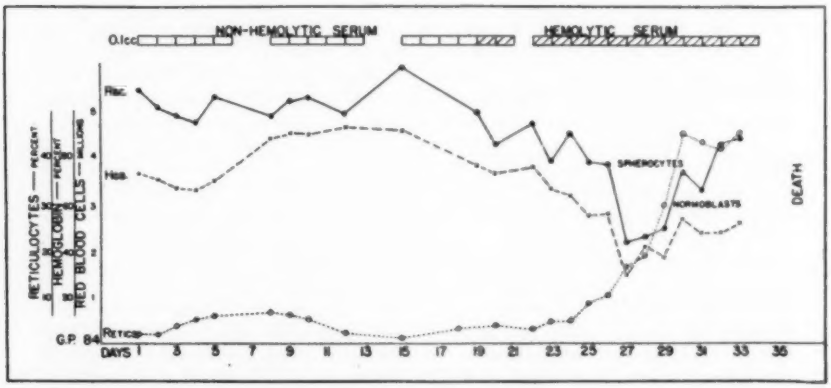


CHART 1.—The effect of (*a*) normal rabbit serum, and (*b*) hemolytic rabbit (anti-guinea pig) serum on the red blood cells and hemoglobin of the guinea pig.

The effect of the normal serum is negligible, whereas the hemolytic serum produces intravascular hemolysis with anemia and a compensatory reticulocytosis.

(*a*) *Large Dosage.* Doses of hemolytic serum varying between 0.5 and 2 cc. were given to 27 guinea pigs. This usually produced death within 5 days. In almost every instance, a fulminating anemia resulted, which was characterized by the presence of an almost uniformly microcytic type of cell population and a greatly increased erythrocyte fragility. Very little evidence of bone-marrow regeneration in the form of reticulocytosis was present, and at postmortem examination hemoglobinuria was a striking feature. In 5 cases a less fulminating acute hemolytic anemia with less marked microcytosis developed.

(*b*) *Medium Dosage.* Nineteen guinea pigs received moderately large dosage: 0.2 cc. of hemolytic serum daily or increasing daily doses of serum beginning with 0.1 cc. up to 0.7 cc. Usually an acute hemolytic anemia resulted, although in 1 case a fulminating anemia developed as with the larger dosage, while in 5 cases a rela-

tively subacute type of anemia ensued. Occasionally definite anemia did not develop. In the majority of these cases, the erythrocyte count dropped to levels of about 1,000,000 in a period of 5 to 7 days. The outstanding hematologic feature in these animals was the development of small, thick red cells ("spherocytes") which became prominent about the 3d to the 5th day after injection. This phenomenon was associated with marked increase in erythrocyte fragility. Within a day or two after the most marked spherocytosis, reticulocytes became prominent, in some cases reaching a level of 50 to 56%, and nucleated red cells appeared. Spherocytes now became diminished both in relative and absolute numbers, and the blood picture became dominated by the appearance of large red cells, usually reticulated. The animals now either made an uneventful recovery or died.

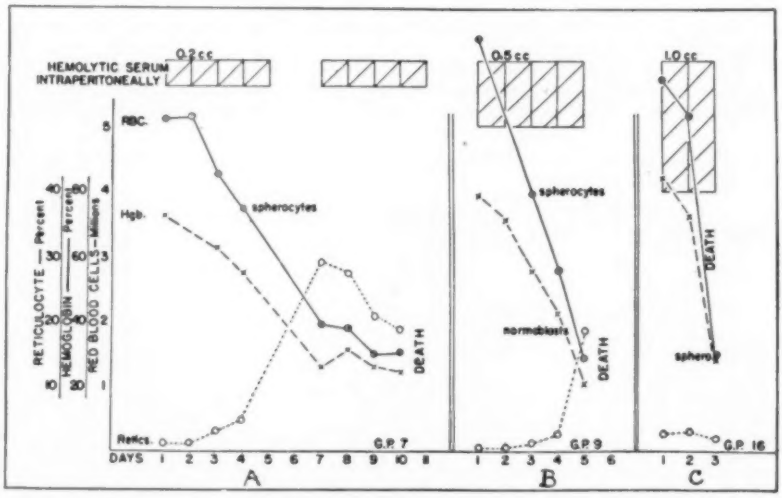


CHART 2.—The effect of varying doses of hemolytic serum on the red blood cells. A small dosage results in (*a*) a gradually progressive anemia with secondary well-marked regenerative changes (reticulocytosis); (*b*) moderate dosage in acute hemolytic anemia; and (*c*) large dosage in fulminating anemia with hemoglobinuria but without reticulocytosis.

(*c*) *Small Dosage.* Eleven guinea pigs were given small doses of hemolytic serum—9 animals 0.1 cc. daily, and 2 animals 0.1 cc. twice weekly. There were no demonstrable effects in the 2 animals of the latter group, whereas in those given daily injection, all developed subacute anemia. The "subacute anemia" which was less rapid in its development than the acute type was similar in its hematologic picture to the terminal reaction of the acute syndrome, *i. e.*, there was moderate anemia of 3,000,000 to 3,500,000, and very little spherocytosis, the blood picture being dominated by the

presence of nucleated red cells, reticulocytes and normal-sized red cells ("pseudomacrocytic" blood picture). In these cases the anemia ordinarily persisted for about 2 to 3 weeks, following which the animal usually made a complete recovery.

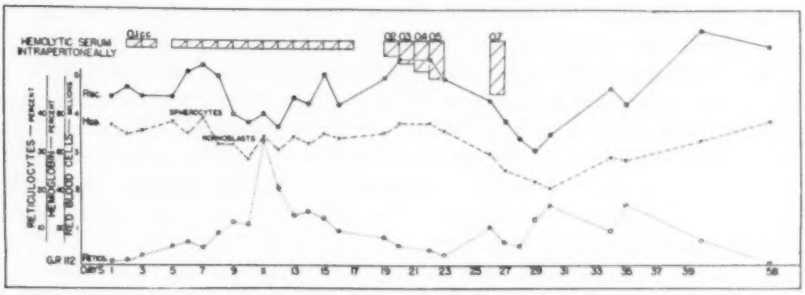


CHART 3.—The effect of increasingly large doses of hemolytic serum after several injections of small daily dosages.

Despite the relatively large dosages, a precipitous drop in red blood cell count does not develop, probably because of the protective action of a previously stimulated bone marrow. This effect may be contrasted with the findings recorded in Chart 4.

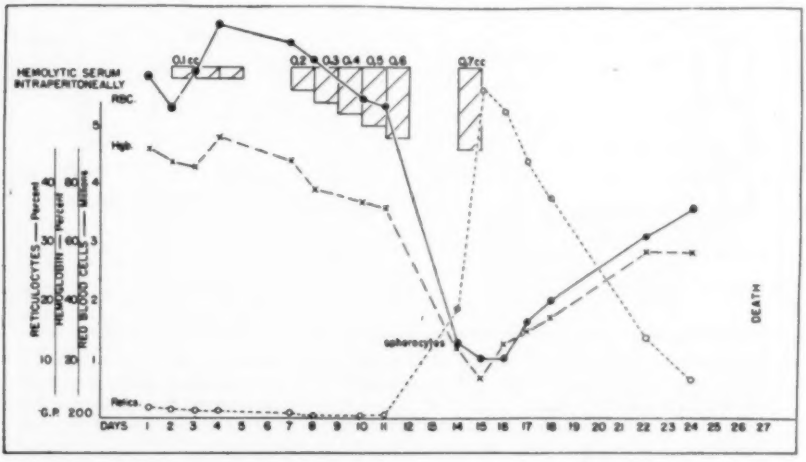


CHART 4.—The effect of increasingly large doses of hemolytic serum. There is a rapid drop both in red cell count and hemoglobin, quite in contrast to the changes noted in Chart 3, in which the animal was given preliminary small doses of hemolytic serum.

(*d*) *The Effect of a Small Dose of Hemolytic Serum Followed by a Large Dose.* In 1 guinea pig, small doses (0.1 cc. 1–50) of hemolytic serum were given intraperitoneally daily for 16 days with the resultant development of subacute anemia (Chart 3). Beginning with the 18th day, the daily dosage of serum was increased by 0.1 cc. until 0.7 cc. was given. This resulted in a moderate degree

of anemia with only slight reticulocytosis (16%), the animal making a complete recovery. This is quite in contrast with the reaction of the animals receiving increasing daily dosage of hemolytic serum up to 0.7 cc., *without* preliminary small injections; in these, the development of acute hemolytic anemia was the rule (Chart 4).

4. *The Blood Picture.* As pointed out above, the blood picture varied directly with the dosage of hemolytic serum injected—a large dose producing a rapidly fulminating anemia with hemoglobinuria, a medium-sized dose producing an acute hemolytic anemia, and a small dose a subacute type of syndrome.

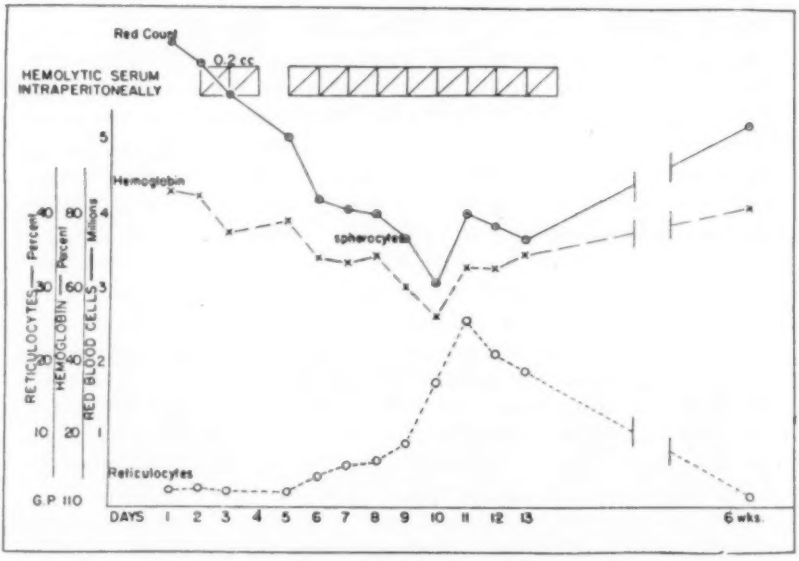
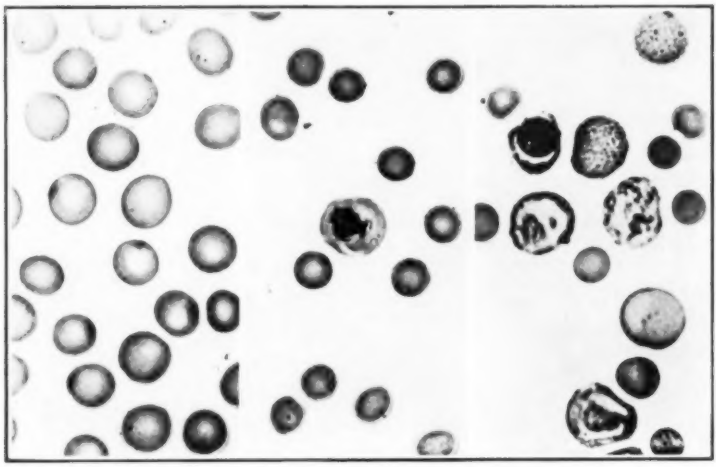


CHART 5.—The effect of moderate daily doses of hemolytic serum. A subacute type of anemia develops. Note the well-marked reticulocytosis which is followed by gradual rise in the erythrocyte and hemoglobin level. Spherocytosis develops with progression of the anemia.

Red Blood Cell Counts. The normal red cell count of the guinea pig varies between 5,000,000 and 6,000,000 per c.mm., and the normal hemoglobin concentration between 13 and 15 gm. per 100 cc. In the fulminating cases the red cell count dropped precipitously. Within 1 to 2 days the count fell to 1,000,000 or less with a concomitant fall in hemoglobin, and the animal died. In the less fulminating cases, the red cell count fell less precipitously, reaching its lowest level of 1,000,000 or thereabouts in a period of 5 to 7 days, following which the animal either died or began to show recovery. In the subacute cases, the development of anemia took place relatively slowly over a period of 7 to 14 days, and the anemia was less profound with the red cell count usually dropping to a level of

about 3,000,000 to 3,500,000. Following the persistence of an anemic level for several days, there was gradual increase in erythrocyte count while the animal made complete recovery (Chart 5).

Type of Red Cells. The red cells of the normal guinea pig are identical in appearance with those of man, being round, and when viewed on edge, biconcave in appearance. There is slight anisocytosis, but the great majority of cells have a diameter between 7 and 7.5 micra, the average red cell diameter being 7.2 micra. With the development of anemia, marked changes in the size and shape of the red cells took place, the most striking change being in the development of microcytosis (Chart 6). The microcytes were further characterized by an appearance of increased thickness, clearly visible in the stained preparations, and unusually well-brought out in the supravital preparations. When seen on edge, these cells presented a striking appearance of roundness, the biconcave appearance having completely disappeared and the cell having assumed a spherical character. Supravital studies on these preparations revealed that the red cell goes through a series of distinct changes before becoming a "complete" spherocyte. At first the biconcavities become more shallow. Then one concavity disappears, leaving cup-shaped or jug-shaped cells with an indentation which becomes progressively more shallow. When this disappears, a round ball-shaped "spherocyte" results. The more sudden and severe the anemia, the greater was the proportion of these cells. In the fulminating cases, the animal died with practically 100% spherocytes, the rare reticulocytes appearing huge in comparison. In those with longer course, the red cell picture shortly became diversified, due to the appearance of large, biconcave, polychromatophilic red cells which, when stained supravitally, were seen to be reticulocytes. At the same time nucleated red blood cells (normoblasts) of varying degrees of maturity and in varying numbers were seen, together with other signs of increased regenerative activity on the part of the bone marrow: basophilic stippling, ring bodies, and so on. The striking contrast between the small thick spherocytes and the immature cells (reticulocytes) was at no time greater than at this point, when both types of cells were present in great abundancy (Chart 7). In this stage both rapid hemolysis and well-marked regenerative activity were present. In cases which went on to recovery the spherocytes gradually disappeared as more and more reticulocytes and new mature red cells appeared, and with their disappearance the blood picture assumed a "pseudomacrocytic" appearance with an actual increase in the average red cell diameter (*q. v.*). This was due to the presence of large numbers of polychromatophilic macrocytes (reticulocytes), and of normal new red cells. With recovery of the animal, the blood picture finally resumed its normal appearance.

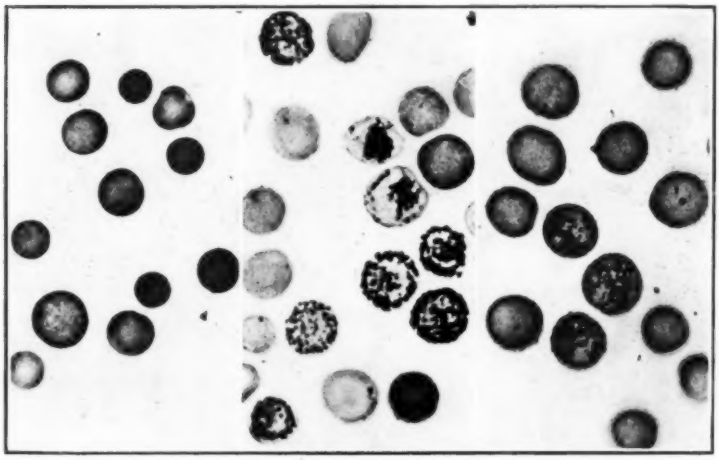


Normal Hemolytic phase Regenerative phase

Acute experimental hemolytic anemia.

CHART 6.—Changes in the erythrocyte picture in the peripheral blood of a guinea pig following daily injection of large doses of hemolytic serum.

The hemolytic phase (4th day) is characterized by the presence of extreme microcytosis (spherocytosis), while the regenerative phase (7th day) is marked by the appearance of large new cells (reticulocytes) which appear huge in contrast. Note that the spherocytes have a thick appearance even in dry films and show no central concavity. (× 940.)



Hemolytic phase Regenerative phase Recovery phase

Subacute experimental hemolytic anemia.

FIG. 7.—Changes following daily injections of moderate doses of hemolytic serum.

The hemolytic phase (7th day) is characterized by a moderate spherocytosis. In the later phases of regeneration and recovery the large reticulocytes give a false picture of macrocytosis ("pseudomacrocytic" picture) similar to that seen in certain cases of clinical acute hemolytic anemia. Note that the new red blood cells (reticulocytes) but recently derived from the bone marrow are large. (× 940.)

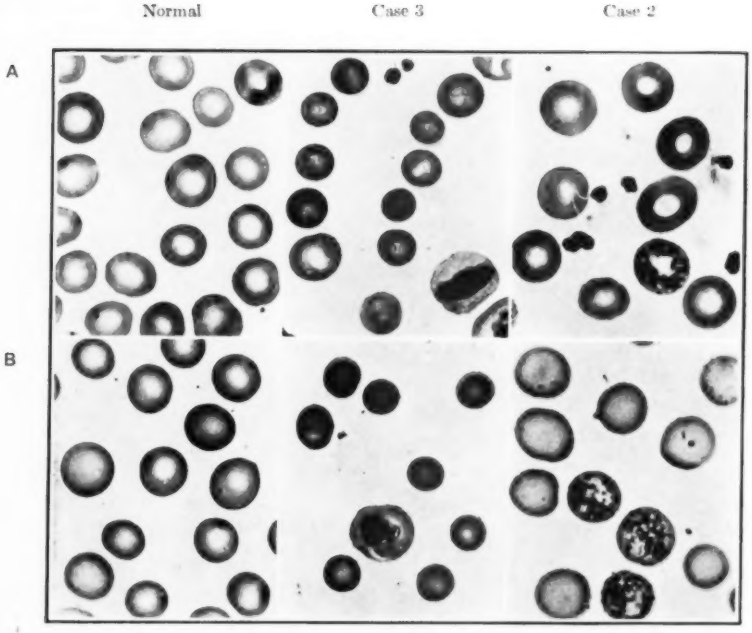


CHART 12.—Similarities in the blood pictures of the guinea pig (*B*) and man (*A*) normally, in acute hemolytic anemia and in subacute hemolytic anemia.

Note the spherocytosis in the middle set of pictures and the pronounced reticulocytosis characteristic of the subacute course both clinically and experimentally. (× 940.)

Reticulocytes. In the acute fulminating cases, the animals frequently died with severe anemia and without the appearance of reticulocytes. The less acute cases were characterized by varying degrees of reticulocytosis, most marked in the subacute cases which

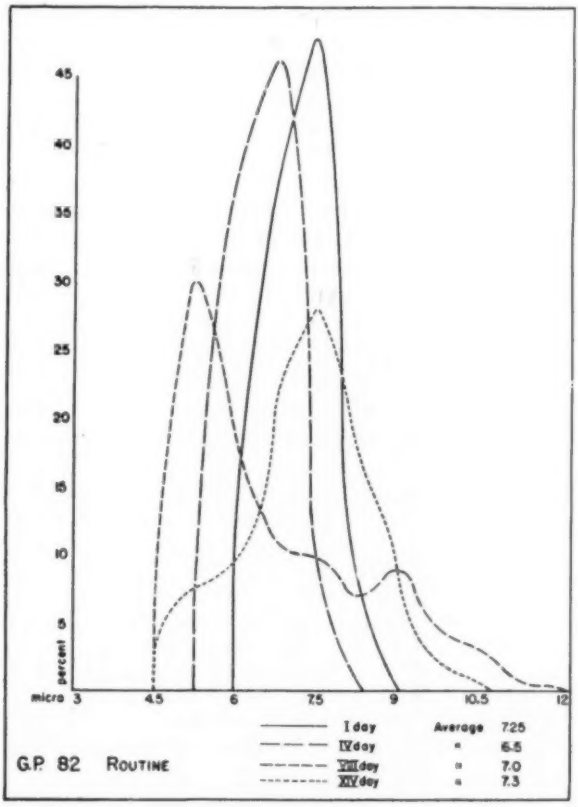


CHART 8.—Price-Jones curves of the red blood cell diameters during the development of anemia following the injection of hemolytic serum.

Note that the first change is a uniform shift (4th day) to a smaller type of red cell population. Next (8th day) is further diminution in the cell size with the appearance of well-marked spherocytosis. Simultaneously one notes the appearance of large cells (reticulocytes) (see also Chart 9). This gives a peculiar "hump"-shaped curve. Finally (14th day) is a shift to a normal type of curve, although a heterogeneity of all the red cell population (wide curve) is still to be noted. (Guinea pig No. 82.)

went on to recovery. In these animals reticulocyte counts of 40 to 56% were common. Following the reticulocyte peak the red count usually rose.

Price-Jones Curves. The varying and often rapid changes in the types of red cells are best brought out in studying the red cell

diameters by the Price-Jones method. The first change which developed became noticeable in 1 to 3 days and was characterized by a shift to a smaller type of mature red cell population, the average red cell diameter diminishing to about 6.8 micra (Chart 8). With further diminution in the average red cell diameter to between 5 and 5.6 micra, anemia became increased. The very small cells

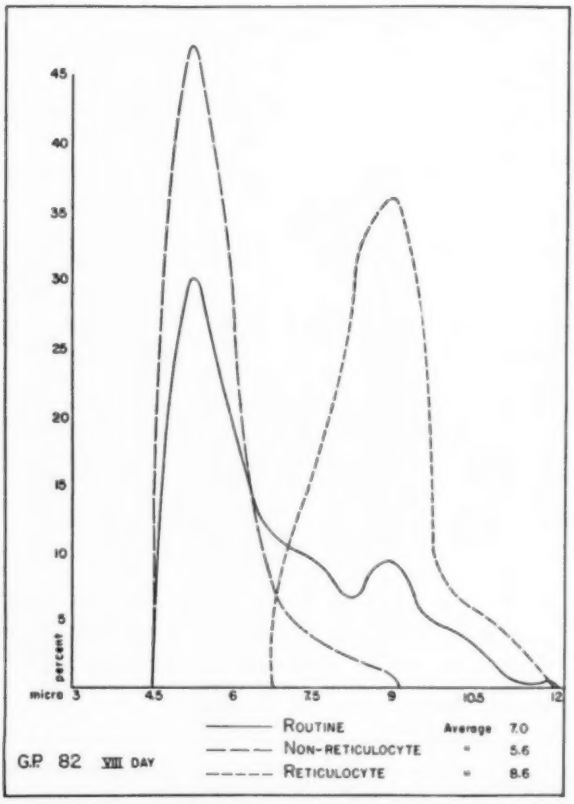


CHART 9.—Analysis of the Price-Jones curve of the red cell population on the 8th day (see Chart 8).

It will be seen that the formerly normal cells have almost entirely been reduced to microcytes (spherocytes) and that the apparent increase in large cells and consequent increase in average cell diameter is produced by the appearance of normal-sized reticulocytes. Guinea pig No. 82.

were all spherocytes. In those animals which survived this period, the next change that occurred was characterized by a double-peaked Price-Jones curve. Analysis of this curve by differential diameter counts of reticulocytes and non-reticulocytes (Chart 9) demonstrated that the largest peak, which was at a smaller cell diameter than normal, was caused by the mature red cells (mostly spherocytes), and the smaller peak, present at a larger red cell diameter

than normal, was composed of reticulocytes. With recovery, the curve might at first show a macrocytic tendency, which then gave way to an essentially normal type of curve.

Hematocrit, Mean Corpuscular Volume, Mean Cell Thickness. The volume of packed red cells of the normal guinea pig varies between 46 and 50%. When a moderately large dose of hemolytic serum was given, a definite diminution in the hematocrit was noticeable within 24 hours, and within 48 hours there was a precipitous drop to levels between 25 and 32%. With the development of severe anemia, the hematocrit value reached levels of between 11 and 20%. The mean corpuscular volume of the normal guinea pig is somewhat smaller than that of the normal human, varying in our cases from 73 to 82 cubic micra. Although the hemoglobin and red cell levels diminished rapidly, no definite change took place in the mean corpuscular volume; in fact, this might actually become increased: from 73 to 89 cubic micra in one instance, from 81 to 87 cubic micra and from 73 to 87 cubic micra in other instances.

Despite this essential lack of change, or even increase, in the total cell volume, the diameter of the red cells was simultaneously diminishing rapidly. This could indicate only one thing: a marked increase in the thickness of the individual red cell. Calculation of the mean cell thickness from the mean cell volume and the mean cell area showed a marked increase in this factor: from 1.79 to 4.2 micra (!) in 1 case in which the animal died with practically all spherocytes, and from 1.9 to 3.01 micra in another instance (Table 1).

TABLE 1.—CORRELATION OF CERTAIN ERYTHROCYTIC FACTORS.

Dose (in cc.).	Days.	R.B.C. (in mill.).	Hematocrit. %	M.C.V.	M.C.D.	M.C.T.	Fragility (% NaCl). B.H.	Fragility (% NaCl). C.H.
G.P. 88. Large Dose—Acute Fulminating Anemia.								
0.3	0	6.90	49.5	73	7.3	1.79	0.40	0.24
0.3	1	5.45	44.5	82	7.0	2.11	0.40	0.26
0.3	2	3.81	28.0	74	6.0	2.70		
	3	2.50	18.0	72	5.8	2.71	0.80	0.32
	4	1.56	14.0	89	5.2	4.20	+0.80	0.40
G.P. 89. Medium Dose—Acute Anemia.								
0.2	0	5.70	42.0	74	7.0	1.90	0.46	0.30
0.2	1	5.04	38.0	76	6.8	2.09	0.48	0.28
0.2	2	4.79	39.0	81	6.6	2.34	0.46	0.28
	5	4.76	38.0	80	5.8	3.01	0.56	0.32
	6	4.39	37.0	84	6.0	2.99	0.58	0.20
	7	4.11	36.0	87	6.2	2.89		
	8	3.89	32.0	81	6.2	2.69	0.52	0.12
	9	4.32	32.0	78	7.1	1.94	0.50	0.12

M.C.V. = mean corpuscular volume.
M.C.D. = mean corpuscular diameter.
M.C.T. = mean corpuscular thickness.
B.H. = beginning hemolysis.
C.H. = complete hemolysis.

With diminishing hematocrit percentage, the mean cell volume remains normal or even increased but the mean cell diameter becomes greatly diminished. Thus the mean cell thickness becomes greatly increased and simultaneously, the fragility of the red cells becomes abnormally great.

Fragility. The erythrocyte fragility was studied in 12 instances. In the normal guinea pig, hemolysis began at 0.4 to 0.5% of NaCl solution, and was complete at 0.2 to 0.3%. Average figures for beginning and complete hemolysis were 0.44 to 0.24%. The fragility test following administration of hemolytic serum varied directly with the amount of serum given, *i. e.*, with the type of hemolytic syndrome induced (Chart 10). In the fulminating cases, with the development of severe anemia, hemolysis began at or just below the concentration of normal salt solution (0.8 to 0.85%), becoming complete at 0.4%. In the less fulminating acute cases, fragility

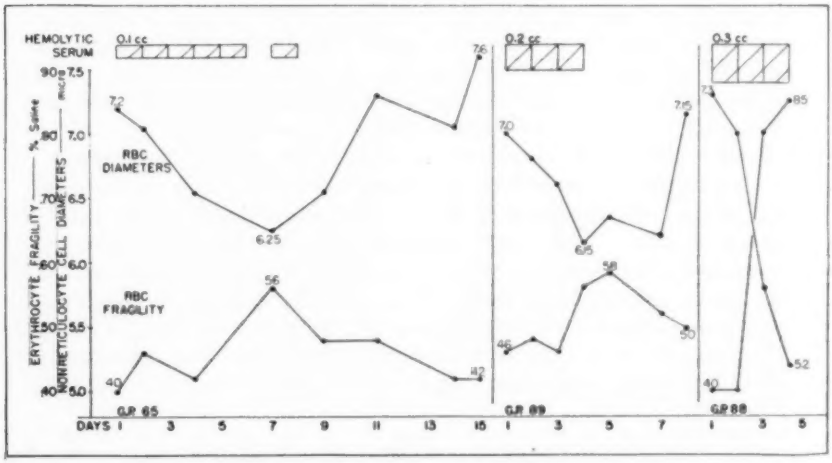


CHART 10.—The effects of varying doses of hemolytic serum on cell diameters and fragility (resistance to hypotonic solutions of sodium chloride) of the red cells. A large dose of hemolysin results in a precipitous drop in the red cell diameter and a greatly increased fragility; smaller doses result in less dramatic changes. In guinea pig No. 65, given the smallest dose, an actual increase in red cell diameter develops in recovery, with an associated return of the erythrocyte fragility to normal. There is striking correlation between the development of microspherocytosis and increasing fragility. The spherocyte (and its associated phenomenon: increased fragility) may be considered as an index of intravascular hemolysis.

rapidly increased to values of 0.58 to 0.68%, following which it would diminish unless the animal died. In the "subacute" cases, fragility became only slightly increased, hemolysis beginning at 0.5 to 0.56%. As the animal recovered, the fragility test returned to its normal level; in fact, in some instances, increased resistance of the red cells developed with hemolysis beginning at 0.38% NaCl and becoming complete at 0.1 to 0.12%.

The changes in fragility test could readily be correlated with the various morphologic changes occurring in the red cells. Thus, with extreme fragility, as in the fulminating cases, almost all of of the red cells were spherocytes; with moderately increased fragility,

the spherocytes were not as numerous; and with slightly increased fragility, relatively few of the cells were present. These correlations are graphically brought out by comparison of beginning hemolysis in the fragility test with the average red cell diameter of the non-reticulocytes (Chart 10). It is seen that increasing fragility varied directly with diminishing diameter of the mature red cells and with their increasing thickness; diminishing fragility developed as the

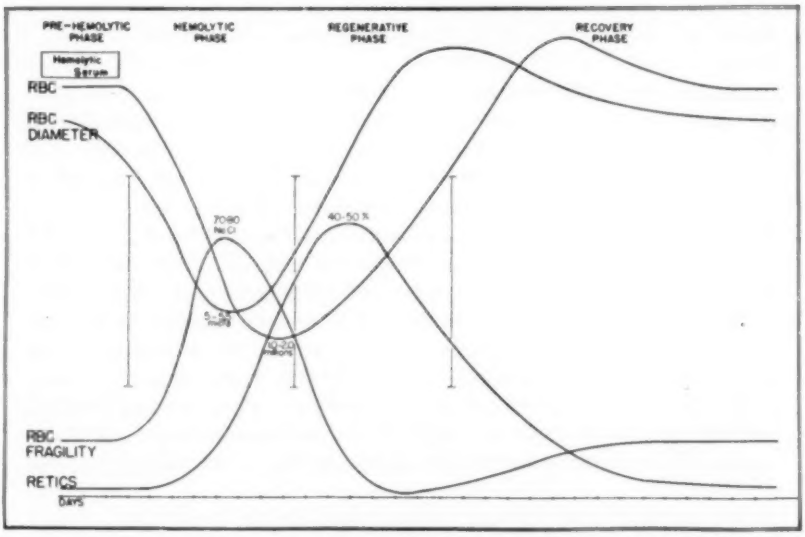


CHART 11.—Semidiagrammatic chart of the various phases which take place in the experimental hemolytic anemia produced by the injection of hemolytic serum. During the "prehemolytic" stage the only demonstrable change is slight diminution in the average diameter of the red cells. This is the stage of "sensitization." Following this (hemolytic phase), as the red cells shrink further and become more markedly spherocytic, there is an accompanying decrease in the resistance of the cells with a rise in the fragility. The spherocytes now begin to disintegrate with resultant fall in the red cell count. As a compensatory measure the bone marrow becomes hyperactive (regenerative phase) and reticulocytes appear. With the appearance of the reticulocytes, there is an increase in the cell diameter, which may actually become greater than normal (pseudomacrocytic blood picture). Simultaneously with the outpouring of new cells, there is a rise in the red cell count. During the period of regeneration when the old (destroyed) cell population is entirely replaced, the resistance of the new cells is found to be increased. The recovery phase is characterized by gradual return of all the factors to their normal levels.

red cell diameter increased. The phase of increased resistance which might develop during recovery was associated with the development of the "pseudomacrocytic" type of blood picture, in which large numbers of reticulocytes and normal new red cells were present (Chart 11).

5. *Pathologic Anatomy.* In the fulminating cases there was evidence of severe "toxicity" with occasional areas of ecchymosis, hemorrhagic areas in the lungs, and reactions of necrosis about the

site of the intramuscular injection. These were lacking in the "acute" and "subacute" cases. The spleen in all types was invariably enlarged—from 1½ to 5 times its normal size—and microscopically showed extreme congestion, with dilatation of sinusoids. The bone marrow was intensely hyperplastic, the hyperplasia being limited mainly to the erythroblastic elements. Erythrogenesis was of the "normoblastic"[17] type, the immature red cells being similar to those seen in functional hyperplasia following hemorrhage. Differential counts of bone-marrow smears bore out the marked hyperplasia, as evidenced by the numerous erythrogones and the normoblasts of the "A" (macroblast) variety.[17] Price-Jones diameter studies of the nucleated red cells of the bone marrow showed that the most mature nucleated red cells (Type "C") were normal in size, even in those animals which had died of the fulminating syndrome with practically 100% of spherocytes present. In other words, the discrepancy in size between the relatively large normoblast "C" (normoblast) of the bone marrow (as well as of the peripheral blood, when present) and the spherocyte of the blood was a striking phenomenon which will be commented upon below.

Comment. 1. *Previous Studies.* The production of hemolytic anemia by the use of heterophilic hemolytic serum is almost as old as the science of immunology. Belfanti and Carbone[2] were apparently the first to carry out this procedure. Bordet,[3] and Ehrlich and Morgenroth[20] used this method in developing their theories of immunity. Cantacusène,[5] and Lesné and Ravaut[35] established the different effects of large and small doses. Panton and Ross,[18] confirmed by Muir and McNee,[39] demonstrated that large doses caused hemoglobinemia and hemoglobinuria, whereas small doses produced nucleated red cells and many microcytes. Banti,[1] in 1913, distinguished two phases in the experimental hemolytic anemia: hemolytic, characterized by diminution in red cell count and hemoglobin; and regenerative, characterized by the presence of large numbers of reticulocytes. Banti also demonstrated the appearance of marked fragility of the red cells which developed as the anemia progressed. From 1913 to 1937 few investigations were apparently carried out with this method. Filo,[23] in 1937, produced hemolytic anemia by the use of heterolytic sera and, although he carefully studied the erythrocyte, leukocyte and platelet counts, he made but little attempt to correlate this work with clinical phenomena, nor did he study the red cell diameter or fragility.

In summary, although previous investigations in the production of various hemolytic syndromes by the use of heterolytic sera have been moderately extensive, they are deficient from the hematologic standpoint in that most of the studies were made as part of an immunologic research. The work of Panton and Ross,[18] Banti,[1] and of Filo[23] is thoroughly in line with our own investigations, although the significance of the various hematologic findings does

not appear to have been appreciated. Thus all but Banti noted the pronounced microcytosis, but failed to attach any significance to it. Banti dismissed the increased fragility by concluding that it was due to the development of a special "fragilizing" activity by the organism. He discounted the possibility that the increased fragility might be due to the action of the hemolysin upon the red cell, as suggested by Troisier, Dufourt and others.[45b] In none of the investigations was the spherocytic character of the red cell or its relationship to the increased fragility mentioned.

2. *Dosage and Classification.* It has been demonstrated that by simple variation in the dosage of hemolytic serum various types of hemolytic syndromes can be produced. Thus large dosage resulted in fulminating anemia and hemoglobinuria; moderate dosage, in acute hemolytic anemia in which initially spherocytosis and later reticulocytosis were prominent; small dosage, in a relatively chronic or subacute anemia, in which bone-marrow regeneration often overshadowed the evidences of hemolysis. These three types were not always as clear-cut as thus delineated, since transition types could occasionally be distinguished. Preliminary experiments in the production of chronic hemolytic anemia in the guinea pig have not as yet been successful.

The various types of hemolytic syndromes experimentally produced may readily be matched with well-known clinical syndromes, often described under different headings, and supposedly completely unrelated. These are compared in the accompanying table:

TABLE 2.—HEMOLYTIC SYNDROME AND DOSAGE OF HEMOLYSIN.

Experimental syndromes.	Clinical syndromes.
Large Dosage.	
A. Fulminating hemolytic anemia with hemoglobinuria	Acute paroxysmal hemoglobinuria;[27,28] paroxysmal nocturnal hemoglobinuria;[12,27] fulminating acute hemolytic anemia with hemoglobinuria; hemoglobinuria with hemolytic anemia.[9]
Moderate Dosage.	
B. Acute hemolytic anemia:	Acute hemolytic anemia ("febrile," "Lederer's");[11,22,25,34,36]
(*a*) With spherocytes predominating.	(*a*) With spherocytes predominating.
(*b*) With reticulocytes predominating	(*b*) With reticulocytes predominating; "crisis" of chronic hemolytic anemia; ? erythroblastosis fetalis.
Small Dosage.	
C. Subacute hemolytic anemia with "pseudomacrocytic" blood picture	Subacute hemolytic anemia[11,22,25,34,36] with "pseudomacrocytic" blood picture (often mistaken for pernicious anemia); hemolytic anemia and "pernicious anemia" of pregnancy.
D. Chronic hemolytic anemia (not yet produced)	Chronic hemolytic anemia: With spherocytic blood picture (congenital); ? with sickle-cell blood picture.

By analogy with the experimental syndromes, one may speculate that differences in clinical syndromes are due, at least in some measure, to differences in the degree of intravascular hemolysis which is taking place. By thinking of the various clinical hemolytic syndromes in terms of "dosage" of hemolysin, one can readily see why hemoglobinuria may accompany certain cases of fulminating acute hemolytic anemia, why hemolytic icterus is an accompaniment of certain cases classified as "hemoglobinuria," and why "crises," resembling in every respect the clinical picture of acute hemolytic anemia, occasionally occur in cases of chronic congenital hemolytic icterus.

Hemoglobinuria is merely the signpost of a hemoglobinemia that rises above the kidney's threshold for blood pigment. Hemoglobinemia develops when intravascular hemolysis is so rapid that conversion of hemoglobin to bilirubin cannot take place rapidly enough to prevent its detection in the blood stream. Chauffard[8] pointed out this fact in 1909 and stressed the relationship of dosage of hemolysin to the character of the resultant syndrome. Thus, in the case of Chauffard and Vincent,[8] in which acute hemolytic anemia was present in association with a very active serum hemolysin, hemoglobinuria and icterus were both present. In paroxysmal "cold" hemoglobinuria (associated with the Donath-Landsteiner type of hemolysin) intravascular hemolysis is apparently so rapid that icterus, which takes time to be produced, does not develop[37] in detectable amounts. In paroxysmal nocturnal hemoglobinuria,[38] hemoglobinuria is outstanding at night whereas during the day only icterus and hemoglobinemia are present. The report of Hamburger and Bernstein,[27] which stresses the relationship between hemoglobinuria and icterus, points out the common fallacy of regarding cases of hemoglobinuria as belonging to an entirely different category from that of hemolytic anemia (icterus). Hemoglobinuria and hemolytic icterus are simply different manifestations of the same fundamental phenomenon: intravascular hemolysis. Rapid fulminating hemolysis causes hemoglobinemia (and hemoglobinuria); less rapid hemolysis results only in icterus (and usually anemia).

3. *The Blood Picture.* (*a*) *General.* As shown above, the variations in the blood picture were directly dependent upon the dosage of the hemolytic serum and upon the phase of the resultant hemolytic syndrome. Thus, with *large dosage* the blood picture in these cases was a purely hemolytic one and completely lacking in regenerative phenomena. *Medium-sized dosage* resulted in (*a*) a hemolytic phase with many spherocytes, and (*b*) a regenerative phase with prominent phenomena of erythrocytic immaturity. *Small dosage* resulted in an inconspicuous hemolytic phase, soon overshadowed by the phenomenon of regeneration, turning gradually to normal.

(*b*) *The Spherocyte.* The most outstanding feature of the blood picture was the development during the hemolytic phase of large numbers of small, thick red blood cells, *i. e., spherocytes.* These cells exhibited all the characteristic criteria: microcytosis, an appearance of increased density and thickness in the stained preparation, a definitely rounded and globular appearance in the fresh preparations with disappearance of the normal biconcavity, a greatly increased thickness with an equally increased volume-thickness index, and finally increased fragility (see below).

The spherocyte was first described as such by Naegeli[40] in cases of congenital hemolytic icterus. He suggested that these cells were pathognomonic of the disease which could thus be designated as "spherocyte anemia" or "globe-cell anemia." Gänsslen[24] made much the same observations, but correlated the spherocyte and increased fragility. Microcytosis (small diameter) had previously been described by Chauffard[10] and numerous other observers. Von Boros[4] was the first to make careful studies of the increased thickness of the microcytes and showed that, although the cells were diminished in diameter, the cell volume was nevertheless normal. This could only be explained by increased thickness. Von Boros also proposed a "thickness index" to indicate the degree of change in thickness. Haden[26] studied these phenomena further and concluded that "Naegeli's conception of microspherocytosis as the fundamental and probably constant inborn error in this disease (congenital hemolytic icterus) seems the correct one." He stated that "the shape of the red cell indirectly represents an anatomic variation from normal," in common with the "tower skull" and other abnormalities. Gänsslen, Naegeli and Haden all concluded that the microspherocytosis indicated a definite bone-marrow defect and was pathognomonic of the disease. Thompson[44] states: "The spherical microcytes . . . . are as pathognomonic of this disease as are the sickle cells, in sickle-cell anemia." On the other hand, von Boros[4] and Heilmeyer[29] state that they have observed the spherocyte in various conditions other than congenital hemolytic icterus.

Our own experience, both in clinical and in experimental cases, is directly contrary to the view that spherocytosis is primarily due to a bone-marrow defect. We were led to the view that spherocytosis might be due to the activity of a hemolytic agent in the serum by the findings in our third case of acute hemolytic anemia,[16] which was characterized by the presence of large numbers of spherocytes and increased fragility (Chart 12). In this case, as the titer of hemolysin diminished, the red cell diameter increased and the erythrocyte fragility became normal. Similar cases have previously been described by Chauffard, Troisier and Girard,[9] and by Widal and Weissenbach.[47] In previous studies of Henstell and Dameshek[31] of the bone marrow and blood in a case of congenital hemolytic

icterus, it was noted that the red cell diameter of the most mature nucleated red cells in the bone marrow averaged 9.84 micra (normal or slightly increased), whereas the average red cell diameter of the peripheral blood was reduced to 6.76 micra. Furthermore, the most mature nucleated red cells in the peripheral blood of the clinical case of acute hemolytic anemia above referred to were of normal diameter: 8.9 micra, as compared with the average cell diameter of the non-reticulocyte red cells of the same day: 6.85 micra. The average cell diameter of the reticulocytes in this case was 8.16 micra, whereas that of the non-reticulocytes (mature red cells) was reduced to 6.18 micra. These clinical findings, demonstrating that the immature red cells of the bone marrow and peripheral blood, were of normal size while the mature red cells were distinctly smaller than normal, could only indicate that the spherocytes were formed not in the marrow but by the action of some agent on circulating red blood cells. Support of these views was given in our animal experimentation.

In the experimental hemolytic syndromes, the number of spherocytes varied directly with the dosage of hemolytic serum, *i. e.*, the larger the dosage, the greater the number of spherocytes. The Price-Jones curves brought out graphically the changes which developed in the mature circulating red cells as hemolysis took place. These changes have been discussed in detail above. The nucleated red cells of the peripheral blood were always normal in size and nucleated microcytes were never encountered. Studies of the red cell diameters of the most mature nucleated red cells of the bone marrow, in animals dying with almost total microspherocytosis of the peripheral blood, gave normal values for the bone-marrow cells. In an animal dying of acute fulminating hemolytic anemia, for instance, the average diameter of the most mature normoblasts was 9.3 micra (normal), whereas there was extreme microcytosis of the peripheral blood with an average cell diameter of 5.2 micra. We feel that these findings show conclusively that: *a*, spherocytes are formed outside of the bone marrow; *b*, spherocytosis develops only in mature red cells; *c*, a hemolytic agent, such as is present in hemolytic sera, is responsible for its development. As a corollary to these views, the ideas that spherocytosis is pathognomonic for congenital hemolytic jaundice and indicative of an inherited bone-marrow defect are cast into question. We have been able to produce spherocytosis in animals by other hemolytic agents, such as distilled water and phenylhydrazine. Price-Jones,[42a] and Kaminer and Rohnstein[32] also noted that microcytosis became prominent during the phase of hemolysis in experimental hemolytic anemia produced by this drug. Banti[1] noted microcytosis and increased fragility in animals given toluol diamine. In clinical reports of hemolytic anemia due to such agents as malaria and sulphanilamide, the microcytosis is pointed out, without much attention being paid

to the phenomenon. For example, careful inspection of the photomicrograph in Harvey and Janeway's[28] recent article on acute hemolytic anemia due to sulphanilamide will reveal the presence of several typical spherocytes.

We feel, therefore, that spherocytosis represents an alteration in the mature red cell brought about by various types of hemolytic agents. In congenital hemolytic icterus, the spherocytosis may be due to the more or less continued action of an hemolysin. The extreme spherocytosis of the crisis of this disease may be due to the sudden liberation of large amounts of hemolysin and the resultant action upon the mature red cell.

(*c*) *The Reticulocyte and the Pseudomacrocytic Blood Picture.* It may be stated as axiomatic that whenever there is increased blood destruction, increased blood formation shortly takes place, unless, of course, the marrow is incapacitated. So much is this the case, that the reticulocytosis of hemolytic anemia is recognized as an important part of the blood picture and of diagnostic significance. In general, the more active the hemolytic process, the more marked is the reticulocytosis. This is brought out in the cases of congenital hemolytic icterus, in which fluctuations in severity of the disease are accompanied not only by changes in bilirubin content of the serum, urobilinogen content of the urine and extent of spherocytosis of the red cells, but also in the percentage of reticulocytes. In certain cases of acute hemolytic anemia, reticulocytosis is often so pronounced as to dominate the blood picture. Since the reticulocytes (polychromatophilic red cells) are always somewhat larger than the mature erythrocytes, the blood smear in these cases will often appear to be that of a macrocytic anemia. Analysis of the type of red cell population by differential Price-Jones curves of reticulocytes and non-reticulocytes shows that the *appearance* of macrocytosis is given by the reticulocytes. Thus in the second of our cases of acute hemolytic anemia (L. G.) (Chart 12), the average red cell diameter was 7.6 micra; the average diameter of the mature red cells (non-reticulocytes) was, however, 7.28 micra, and that of the reticulocytes 8.33 micra. The mean corpuscular volume in this case at the same time was definitely elevated—125 cubic micra. We have called this type of blood picture "pseudomacrocytic," since, although it resembles superficially the blood picture of pernicious anemia, it is not truly macrocytic in the same sense.

This pseudomacrocytic type of blood picture was readily reproduced in our animal experiments and was noted in the phases of regeneration and beginning recovery (Chart 12). One may conclude from the animal experiments that the finding of a similar picture in the clinical cases is indicative of active hemolysis with simultaneously active regeneration on the part of a functionally hyperplastic marrow.

(*d*) *The Fragility Test.* Chauffard,[10] in 1907, was the first to demonstrate that the red cells of congenital hemolytic icterus were unusually fragile to hypotonic salt solutions. He felt that this was the fundamental abnormality of the disease. The nature of the increased fragility was for many years a mystery. Troisier,[45] Dufourt[19] and others felt that the increased fragility might be due to "sensitization" of the red cells by hemolysin with consequently increased fragility. Banti, who produced experimental hemolytic anemia and demonstrated increased fragility, was at a loss to explain this phenomenon and suggested that the animal developed a "fragilizing" quality in the process. Gänsslen[24] was the first to suggest a definite relationship between the presence of spherical erythrocytes and increased fragility. Haden's[26] investigations confirmed this work and placed it on a firm basis. He further emphasized the direct correlation between thickness of the red cells and their susceptibility to hemolysis. Ponder,[41] and Castle and Daland[6] studied the problem extensively. These recent investigations have abundantly shown both that the increased fragility of the erythrocytes in congenital hemolytic icterus is due to their spherical nature, and that the extent of spherocytosis is directly correlated with the volume-thickness index.

Previous studies of the dynamics of the problem have always been made either by producing spherocytosis *in vitro* by the use of hypotonic solutions or from study of several cases of congenital hemolytic jaundice with variable cell thicknesses. In our own experiments a more dynamic method was utilized, in that we were able to study the changing fragility simultaneously with the changing relationships in the red cell count, red cell size and reticulocyte percentage. As already pointed out above, these studies have shown a striking correlation between the development of spherocytosis and increasing fragility. The red cells become unusually susceptible to hemolysis by hypotonic salt solutions when their average diameter is reduced and their average thickness increased. On the other hand, with increasing cell diameter and diminishing cell thickness, the cells became more resistant to hemolysis. Finally, with the development of a "pseudomacrocytic" blood picture in which reticulocytes were the outstanding cells, the red cells actually became more resistant than normal to hypotonic salt solution.

These results are confirmatory of the previous investigations referred to above. In addition, they have the advantage of having been performed in the experimental animal, where with rapidly altering conditions in the type of red cell present the fragility test could be frequently carried out. They confirm conclusively that the fragility test is merely an expression of the average thickness of the red cell. The increased resistance of the red cells which developed during the phase of marked reticulocytosis is interesting in view of the many contradictory opinions which have been ad-

vanced regarding the fragility of the reticulocytes. As Daland and Zetzel[14] have pointed out, opinion is about evenly divided that the reticulocyte is (*a*) more resistant and (*b*) less resistant than the normal red cell. Our investigations show quite clearly that the reticulocyte is more resistant than the normal red cell. Further studies on this point are now in progress.

The studies of Gänsslen[24] and of Haden[26] showed that increased fragility is a function of the spherocyte. Our own investigations have further demonstrated that spherocytosis is a function of the action of hemolytic agents. We feel therefore that increased fragility is indicative of a hemolytic process and not simply evidence of an anatomic peculiarity of the red cell.

4. *The Relationship of Hemolysins to Hemolytic Anemia.* That various syndromes closely comparable to those seen clinically can be produced by hemolytic sera has been demonstrated. The question may be raised whether the experimental types necessarily bear any significant relationship to the clinical cases. We feel that although there is no proof of the identity of the clinical and experimental syndromes, the evidence is in favor of such a concept. We cite the following: 1, The serum in our 3 cases of acute hemolytic anemia showed the presence of an active "immune" hemolysin which disappeared as the patient recovered. 2, The hemolytic serum used in our experiments corresponded in every immunologic respect to the serum of our clinical cases. 3, The experimental hemolytic syndromes were similar in every respect to the clinical types. 4, Hemolysins have been found in various hemolytic syndromes.

1. Our finding of active isohemolysins in 3 cases of acute hemolytic anemia was a rediscovery, since Chauffard and Troisier,[7] Chauffard and Vincent,[8] Widal and his collaborators,[48] and several others[46] had pointed this out in the years between 1907 and 1914. Krumbhaar,[33] in his review of the subject, published in 1915, referred to these findings. Furthermore, both Chauffard[9] and Widal[47] had observed single cases in which, with diminution in titer of hemolysin, there was subsidence of anemia and diminution in the abnormal fragility of the red blood cells. This fact in Case 3 of our series led to the speculation that the hemolysin might be etiologically related to the disease and the cause of the spherocytosis. The finding of hemolysin in the serum might simply be due to the production of an excess in the tissues with resultant overflow into the blood. The hemolysin which was present gave all the reactions of an immune body and had thus been probably produced in response to an unknown antigen.

2. The hemolytic serum produced experimentally by the injection of guinea-pig erthrocytes into the rabbit possessed all the various characteristics of immune hemolysin and was thus immunologically identical with the human hemolytic serum of the clinical cases.

The same reactions took place in both sera with heat, addition of complement and addition of normal serum.

3. The experimental syndromes which could be produced by varying the dosage of hemolytic serum were identical with various clinical syndromes (see Table 1). Hemoglobinuria, acute fulminating hemolytic anemia, subacute hemolytic anemia could all be reproduced. Although similarity of syndrome does not necessarily indicate a similar etiologic agent, it is nevertheless suggestive, especially when the experimental hemolytic serum is comparable immunologically to that found clinically. The further findings in the experimental cases of spherocytosis, increased erythrocyte thickness and increased fragility together with the development of reticulocytosis, "pseudomacrocytic" blood picture and splenomegaly, were all confirmatory of our main thesis that the various features of the hemolytic anemias are all due to the action of hemolysins.

4. Hemolysins have been found in various clinical hemolytic syndromes. In all, five types of hemolysins have been described: 1, That of paroxysmal hemoglobinuria, in which, as Donath and Landsteiner[37] pointed out, an hemolysin activated by cold was present; 2, that described by Salén[43] in a case of paroxysmal hemoglobinuria as heat stable and not requiring complement; 3, that of paroxysmal nocturnal hemoglobinuria in which, as described by Dacie, Israëls and Wilkinson,[12] a heat-labile, non-complement requiring hemolysin was found in low titer; 4, Enneking's[21] autohemolysin and isohemolysin in paroxysmal nocturnal hemoglobinuria; 5, and finally, the heat-stable, complement-requiring immune hemolysin described by Chauffard and his collaborators and by the present authors in cases of acute, non-familial hemolytic anemia.

Summarizing this line of thought, since hemolytic syndromes identical with those seen clinically may be produced experimentally by immune hemolytic serum, and since hemolysins are occasionally found in clinical cases, the possibility exists that the various clinical hemolytic syndromes are due to the action of hemolysins. These may be of different types and may be present in different amounts. They may function slowly, and produce a relatively chronic process; or violently, and produce a hemolytic "crisis." That the various hemolytic syndromes are due fundamentally to the activity of hemolysins upon mature circulating red blood cells and not to altered cellular formation in the bone marrow has not been definitely proven, although the evidence cited above indicates that the latter possibility is extremely remote.

Summary. 1. Isohemolysins of the immune-body type were discovered in the serum of 3 cases of acute hemolytic anemia.

2. Anti-guinea pig hemolytic serum was prepared by the injection of guinea pig red cells into rabbits. This serum possessed all the immunologic properties of the serum found in the clinical cases.

3. Hemolysis of the red cells of the guinea pig *in vivo* followed the injection of this serum.

4. By varying the dosage of anti-guinea pig hemolytic serum, various types of hemolytic syndromes were produced: fulminating hemolytic anemia with hemoglobinuria, acute hemolytic anemia and subacute hemolytic anemia.

5. Various types of blood pictures could be reproduced at will: microspherocytosis, increased erythrocyte fragility, reticulocytosis, "pseudomacrocytic" blood picture and so on.

6. The spherocyte is a small thick red blood cell unaltered in volume though small in diameter and unusually fragile to hypotonic salt solutions. Our observations point to the conclusion that spherocytosis is due to the activity of hemolysin and not to an abnormal anatomic peculiarity or to a disturbed formation of cells in the bone marrow. Since increased fragility is a function of the increased thickness of the red cell, it is dependent upon the same cause.

7. We believe that hemolytic syndromes are due to hemolysins, possibly of different types and present in different amounts, functioning slowly in some cases and violently in others. The various blood pictures of the hemolytic anemias, *viz.*, anemia, spherocytosis, increased fragility, reticulocytosis, are in all probability due to the effects of the varying activity of hemolysins, and modified by the individual's power to react.

8. Since the experimentally produced hemolytic syndromes and the numerous clinical types are closely comparable, the chief differences in the clinical syndromes may be a matter of the amount of functioning hemolysin present.

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PAROXYSMAL HEMOGLOBINURIA.

With Report of a Case.*

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The subject of this communication (1473–36) is a sailor, aged 33, who reported to the Outpatient Department of the Montreal General Hospital in March, 1936, because of severe chills followed by the voiding of wine-colored urine.

Clinical History. The family history was not relevant.

The patient himself had smallpox at the age of 17 and a gonorrheal urethritis at 24, but otherwise enjoyed perfect health. He denied syphilis by name or symptom.

The illness for which he sought treatment began in the autumn of 1935. Following exposure to cold, he had a shaking chill lasting an hour, followed on 2 consecutive occasions by voiding wine-colored urine. Since the initial attack he has had 5 or 6 rigors, each following exposure to the cold. Subsequent chills were more severe than the first. The attacks lasted from 3 to 4 hours, were characterized by chattering of the teeth and all the usual phenomena of a severe rigor. They were not at once relieved by blankets or the external application of heat. Each chill was followed by the voiding of 1, 2 or 3 specimens of wine-colored urine. At no time was there frequency, burning or painful micturition. He lost 14 pounds during the winter but considered his health normal in the intervals between attacks.

Physical examination was negative in every respect. There was no obvious anemia; no adenopathy; no enlargement of liver or spleen, and the

* Read by title before the Association of American Physicians, May 5, 1936, by the late Prof. Campbell P. Howard.

heart and lungs were normal on both physical and skiagraphic examinations. The blood pressure was consistently low, averaging systolic 90, diastolic 40. There were no stigmata of syphilis. The urine examination on admission was quite normal but the blood Wassermann test was strongly positive. Blood urea, creatinine, sugar and cholesterol were within normal limits. The Van den Bergh was 0.2 units and the urine urobilinogen present in less than one-tenth dilution—both normal values. Pyelograms showed the kidneys to be normal in size, shape and position.

During the patient's stay in the hospital typical attacks were produced by chilling the hands and feet in ice water for 30 minutes. Shorter periods of chilling or chilling of hands or feet alone failed to produce an attack.

The presence of autohemolysins in blood plasma was demonstrated by means of the Donath-Landsteiner reaction. This test consists in chilling a mixture of the patient's serum (inactivated), a dilute suspension of his washed erythrocytes, and complement (guinea-pig's serum), for a period of 10 minutes. When the mixture is heated to body temperature hemolysis occurs if autohemolysins are present. The same mixture unchilled does not show hemolysis.

The first Donath-Landsteiner test on the patient was made on March 16 shortly before the initial experimental chilling which consisted in immersing his hands and feet in ice water for 30 minutes. The blood serum was normal in appearance. The mixture of inactivated serum, washed cells and complement was chilled for 10 minutes in ice water then incubated for 15 minutes at 37° C. No hemolysis occurred. Following immersion the blood serum became bright red in color and showed spectroscopically the bands of oxyhemoglobin. The urine at the end of the period of exposure was clear but 5 minutes later it was brown in color; 30 minutes later it was port-wine colored. This dark color began to clear in 3 hours and the specimen voided 4 hours after immersion was clear. No red cells were present in the urine specimens, though the benzidine test for blood was strongly positive. Spectroscopic examination showed that the red color of the urine was due to hemoglobin. On March 20, 4 days later, the Donath-Landsteiner test was repeated, the routine of the test being altered as in Table 1:

TABLE 1.—DONATH-LANDSTEINER TEST, MARCH 20, 1936.

Test mixture.	Ice-water chilling.	Warming.	Result.
I. Patient's serum — washed R.B.C.—Comp. . . .	None	37° C. 2 hrs.	No hemolysis
II. Patient's serum — washed R.B.C.—Comp. . . .	10 min.	37° C. 2 hrs.	Half R.B.C.s hemolyzed in 2 hrs.
III. Patient's serum — washed R.B.C.—Comp. . . .	30 min.	37° C.	Immediate complete hemolysis
IV. Patient's serum—Group IV R.B.C.—Comp. . . .	13 min.	37° C. 2 hrs.	Incomplete hemolysis
V. Patient's serum—Group IV R.B.C.—Comp. . . .	30 min.	37° C.	Immediate complete hemolysis

The Donath-Landsteiner test of March 20 showed not only that the patient's blood serum contains autohemolysins, that is, hemolysins for his own erythrocytes, but also that the serum will cause hemolysis of any other red cells in the same group. It contains isohemolysins as well as autohemolysins. It demonstrated further that the technique of the test must be altered to meet varying degrees of susceptibility to chilling. In this instance the test carried out on March 16, according to approved technique, was quite negative. By lengthening the time of chilling of the blood serum

TABLE 2.—CHANGES OCCURRING *e Frigore* AND AFTER A CHILL.

Time.	Urine.							Blood.																Fragility R.B.C.s.
													Differential.											
	Appearance.	Sp. gr.	React.	Alb.	R.B.C.	Benz.	Micr.	R.B.C.	W.B.C.	Hb.	Platelets.	Cell diam.	P.	Ly.	Eos.	Mono.	Cell vol.	Sed. rate.	Plasma color.	Van den Bergh.	Liver.	Spleen.	Temp.	
9.55 .	Yellow	0.14	Ac.	0	0	0	0	4.09	16.1	93	183	7.7	75	18	3	2	45%	0.6 mms.	Light yellow	0.2	0	0	98[2]	0.475 to 0.375
9.55*																								
10.35 .	Amber	...	Ac.	+	0	2+	0	...	...	..	..	..	..	..	..	..	...	....	.....	..	0	0	98[2]	
10.35†																								
11.00 .	Dark wine	...	Ac.	3+	0	4+	Many gran. casts	3.64	8.5	80	..	..	68	28	1	1	42%	0.45	Light red	1.0	....	....	96[3]	0.475 to 0.375
11.00‡																								
12.00																								
1.00 . .	.....	...	..	..	..	..	....	3.65	17.8	82	141	7.7	87	9	1	1	...	....	Red	..	Palp.	Palp.	100[3]	
3.00 . .	Brown red	0.04	Ac.	+	0	3+	Few gran. casts	...	...	..	..	..	..	..	..	..	...	....	.....	..	Palp.	Palp.	99[3]	
5.00 . .	Amber	0.00	Ac.	+	0	Tr.	Occ. gran. cast	...	...	..	..	..	..	..	..	..	...	....	.....	..	Palp.	Palp.	99[3]	
7.00 . .	Yellow	0.06	Ac.	Tr.	0	0	0	...	...	..	..	..	..	..	..	..	...	....	Yellow	..	0	0	97[4]	

* Hands and feet immersed in ice-water for 35 minutes.
† Chill developed with generalized shaking and chattering of teeth. Exposed parts white. Vessels constricted.
‡ External heat applied.

in the second test on March 20 the result was strongly positive. These findings agree with the clinical observations that chilling of one arm and one foot, or even the two feet or two hands, was insufficient to bring about a rigor. Definite chilling of both hands and feet was necessary to produce an attack.

The dramatic nature of the onset of the chill and the changes which took place during the rigor are briefly summarized in Table 2. It is to be noted that hemoglobinuria was present slightly before the time of onset of the chill and before external heat was applied. At no time were red cells found in the urine, though the benzidine test on the pigmented specimens was strongly positive and the spectroscope showed the bands of oxyhemoglobin. The presence of albumin and granular casts during the excretion of the hemoglobin may indicate that the latter had an irritant effect on the kidneys during excretion.

The patient subsequently received one 3 months' course of antiluetic therapy, then disappeared for a year. During that interval of time no chills occurred, although he spent the winter in Montreal.

Discussion. The disease is seldom encountered. Only 1 other case was found in the records of the Montreal General Hospital between the years 1898 and 1936 during which time there were 209,879 admissions. A majority, though not all cases, have syphilis.

The history is characteristic. The patient experiences rigors after chilling which are, however, not followed by any great degree of fever. Wine-colored urine is noted commonly at the first voiding after the chill and it persists for some hours. After the cessation of hematuria no symptoms are experienced until again exposed to chilling.

Physical examination, if made between attacks, reveals no characteristic abnormality. After severe chills slight to moderate anemia of the orthochromic type is commonly present. In our case, after 2 recent rigors, the erythrocyte count was 4.09 millions. During the third chill, reported in detail here, the erythrocyte count dropped from 4.09 to 3.65 million per c.mm. Roughly estimated, this represents a destruction of approximately 10% of the total circulating erythrocytes, and gives some idea of the degree of hemolysis. That this hemolytic upheaval is intimately associated with the reticulo-endothelial tissues is suggested by the temporary enlargement of liver and spleen during and immediately after the chill. The diagnosis in suspected cases can be made with certainty by one or other of the methods employed in our case. The attacks can be produced experimentally by chilling hands and feet in ice water. Prolonged chilling of both hands and feet may be necessary in mild cases. Confirmation of the character of the pigment in blood and urine is obtained by means of spectroscopic examination. The Donath-Landsteiner reaction is positive in all cases. It should be recognized, however, that some modification of the established technique may be necessary in mild cases to fix the antibodies to the erythrocytes. This point has already been referred to in this report.

‡ External heat applied.

Treatment in the syphilitic cases consists in vigorous antiluetic therapy. As in our case, it is usually successful in preventing or diminishing the number of attacks. Dickson[1] reported a case which remained well for at least 13 years after antiluetic treatment.

The nature of the changes which take place during the rigor and the exact mechanism of their production are not definitely known. During chilling of the hands or feet constriction of the cooled skin vessels brings about sufficient slowing of the blood stream to permit lowering of the temperature of the blood in the constricted vessels to a point not greatly above that of the skin. When the temperature of the blood in the capillaries of the chilled extremities is sufficiently reduced, the antibodies become attached to the erythrocytes. Hemolysis occurs when these red cells leave the cooled areas and are warmed to body temperature. This is precisely what happens *in vitro* during the Donath-Landsteiner test. The abolition of the hemolytic process during the spinal anesthesia or after section of the sympathetic nerves to the chilled parts,[2] which presents vasoconstriction during chilling, is further proof of the foregoing hypothesis.

Summary and Conclusions. 1. A case of paroxysmal hemoglobinuria *e frigore* is reported.

2. The disease was apparently arrested by antiluetic therapy.

3. The technique of the Donath-Landsteiner reaction should be modified to meet varying degrees of susceptibility to chilling.

4. Temporary enlargement of liver and spleen may occur during the attack.

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THROMBOSIS—A MEDICAL PROBLEM.

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Whereas thrombosis (including embolism therefrom) has long been accepted as a hazard in surgery, trauma, and obstetrics, its recognition as an equally important hazard in the management of strictly medical patients seems tardy and inadequate. At this hospital its not infrequent occurrence among patients on the medical service impelled a review of the hospital's experience with this condition. Sudden death of a normally convalescent surgical patient on the 10th postoperative day with postmortem disclosure of a massive pulmonary thrombosis merely revealed a dreaded but not unfamiliar manifestation of this surgical hazard. Sudden death

of a medical patient, like Case 35:115, who had undergone three major operations on previous admissions without thrombosis, while currently hospitalized on the medical service for arthritis, with postmortem disclosure of a similar pulmonary thrombosis, demonstrated its less familiar independence of surgical provocation. Such occurrences resulted in the compilation of data on all cases of thrombosis (and embolism therefrom) which had come to postmortem examination during the first 13 years of the hospital's existence (October 2, 1924, to October 2, 1937).

During this period 2613 postmortems were performed averaging 201 yearly, and representing 70% of all deaths in the hospital. Under the technique routinely employed, and with frequent restrictions regarding the head, cord, or other areas, possibly some thrombi (particularly cerebral, portal, popliteal) remained undetected. Thrombosis of the hemorrhoidal plexuses, probably the most frequent site of spontaneous thrombi in human beings was not included, nor were minor thrombi, except when their site lent them importance, as in the coronary or cerebral vessels. Yet in spite of any restriction of method and of limited postmortem examination, and the exclusion of minor thrombi, the condition was encountered in 648 patients—approximately one-quarter of the entire postmortem series. There were 427 strictly medical patients, only 195 were surgical, and 26 comprised a miscellaneous group of obstetric, traumatic, fracture, dislocation and dental cases.

Some mention should be made of the selectivity of patients and diseases in this hospital. Relatively, the hospital admits more old, chronic, rural, cardiac, neoplastic and surgical cases, and fewer young, acute, urban, obstetric and traumatic cases than the average general hospital. The average age at death within the hospital has dropped during 13 years until now it is 7 years below that for the state generally. The main causes of death within the hospital—cardiac, cancer, pneumonia—coincide with those for the state and nation as a whole. In considering therefore whether the findings are typical or merely locally peculiar, these qualifying circumstances should be borne in mind.

To show more clearly the incidence, distribution, and importance of thrombosis among the three classes of patients data on these items have been collected into the large Table 1. Many findings have been omitted which may have been interesting in other respects but proved irrelevant to the objective of portraying thrombosis as an increasingly apparent medical menace. Some of the general characteristics of thrombosis not incorporated in the chart will be briefly considered, followed by some of its contradictory characteristics.

General Characteristics. 1. *Incidence.* The most surprising characteristic of thrombosis is its frequency. Finding 648 cases among 2613 autopsies gives a higher percentage (24%) than in most series.

Bela,[3] in 6581 postmortems between 1913 and 1933 at the City Hospital, Kiel, Germany, found 926 cases (14%); Cleland[6] found 190 cases among 3000 autopsies at Adelaide, Australia (6.3%); Wantoch,[23] 367 cases among 4739 posts at Basel, Switzerland (7.7%). However, coronary thromboses were included in this series, and a complete microscopic examination was made in all cases.

TABLE 1.—THROMBOSIS AND EMBOLISM AMONG 2613 POSTMORTEMS, WISCONSIN GENERAL HOSPITAL, 1924 TO 1937.

	Medical cases.	Surgical cases.	Miscellaneous cases.*	Total cases.
Number of cases:	427.	195.	26.	648.
Sex:				
Male	287	140	16	443
Female	140	55	10	205
Size:				
Gross	300	118	19	437
Microscopic	127	77	7	211
Number:				
Single	265	135	16	416
Multiple	162	60	10	232
Main sites:				
Pulmonary	226	98	17	341
Cardiac (mural)	117	23	..	140
Pelvic	48	23	3	74*
Aorta	40	12	4	56
Inguinal (ileo-femoral)	33	13	6	52
Coronary	36	4	..	40
Renal	24	13	..	37
Cerebral	16	4	3	23
Operative site	...	29	..	29
Miscellaneous	88	40	..	128
Associated diseases:				
Cardiac: primary	203	5	..	208
secondary	135	94	7	236
Cancer	96	90	1	187
Blood dyscrasias	11	1	..	12
Infection: present	114	112	10	236
absent	313	83	16	412
Effect:				
Incidental finding only	165	94	11	270
Morbidity of varying degree	141	63	6	210
Fatal: with sudden death	70	23	5	98
without sudden death	51	15	4	70
With record of previous surgery without thrombosis	142	75	1	218

* Of the 26 patients composing this group, 5 were obstetrical cases, 12 had fractures, 2 had teeth extractions, and 7 had various other types of trauma.

Probably equally as surprising is its preponderance among strictly medical cases. Two-thirds (427) of the cases were medical patients unexposed to the hazards of surgery, obstetrics, or trauma, on the current admission. The fact that 142 of them had previously undergone operations without thrombosis and 19 more gave records of uneventful pregnancies or fractures should not be overlooked.

Classifying patients solely as "medical," "surgical" or "miscellaneous," while desirable for the sake of simplicity, nevertheless continually entails difficulties. The following cases illustrate these

difficulties: Case 35:101, recumbent for 4 months following operation, dies suddenly of pulmonary thrombosis. Shall the operation (surgical factor) or the prolonged recumbency (medical factor) be indicated? Case 35:118 dies later in the day following a craniotomy for brain tumor, with the disclosure at postmortem of a large potentially dangerous inguinal thrombosis. Shall the severe operation or the mechanical pressure of Poupart's ligament plus other local factors be blamed? While these and similar cases were all placed in the surgical classification, they nevertheless indicate the difficulty of making clean-cut classifications, and the importance of medical, or non-surgical factors in postoperative thrombosis.

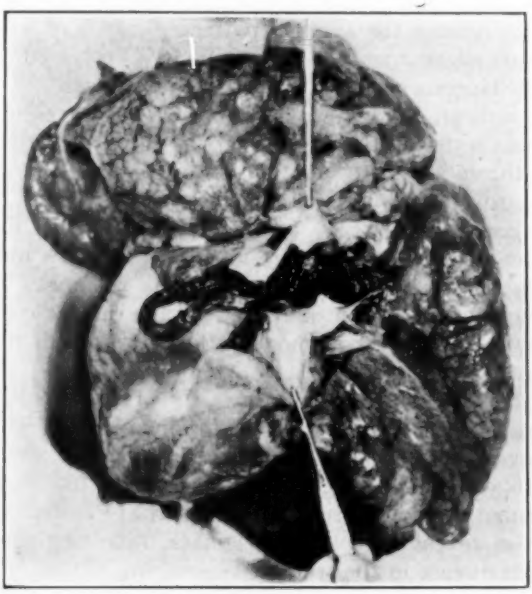

FIG. 1.—Massive pulmonary embolism. Pulmonary artery opened to show, coils of a long laminated thrombus.

Attempts to compute the incidence of thrombosis among the three types of patients (medical, surgical, miscellaneous) also proved unsatisfactory. The postmortems, for example, represented only 70% of the deaths. In view of the many postmortem cases in which thrombosis was disclosed as an incidental, or at least a non-fatal finding, it seemed fair to assume that it had also occurred frequently in patients who recovered. During the period of 13 years covered, there were 99,469 admissions to the hospital, 68,260 operations, and 2142 deliveries; the exact number of casts applied was not available but very probably exceeded 20,000.

2. *Associated Diseases.* One answer to the question why a patient who has undergone surgical operation without thrombosis on a previous admission now dies of thrombosis on the medical service without surgery lies in the main associated condition, namely, cardiovascular disease. In the medical group, 203 patients out of 427 had various types of cardiac disease as the primary condition and 135 more as an important secondary condition. In the surgical group, 5 patients had a primary cardiovascular condition and in 94 more it was an important secondary condition. The disproportion between the two groups in the number of cardiac thrombi is striking. Among the medical patients, many of whom had serious primary heart ailments, 117 out of 427 (28%) revealed this type of thrombosis, the relationship of which to cardiac disorders is well established. Among the surgical patients, only 5 of whom had a primary heart ailment, only 23 out of 195 (8%) revealed it. Among the 26 miscellaneous patients, there was not one case.

Another indication of the relationship of cardiovascular disease to thrombosis is that of the 218 patients in the entire series who now developed thrombosis after avoiding it in previous operations, 179 now had cardiovascular disease as the primary or an important secondary condition. Case 35:278 affords a simple illustration: this 50-year-old male underwent an appendectomy uneventfully 2 years ago; 1 year ago he contracted acute rheumatic fever with cardiac involvement; now hospitalized for the cardiac condition, he dies suddenly of bilateral pulmonary thrombosis with three mural thrombi in the right auricle.

Among the entire series of 648 cases, the principal cardiac lesions were found to the following extent: decompensation with chronic passive congestion of viscera, and so forth, 336 cases; cardiac hypertrophy, 316 cases; hypertension on admission, 153 cases; old or recent rheumatic inflammation of the heart, 114 cases. Only 23 of the 648 cases revealed syphilitic stigmata, reflecting the low incidence of this disease in the state of Wisconsin.

While the preponderance of cardiovascular disease throughout the series tends to simplify the problem, certain other conditions tend to complicate it. In contrast to the abundance of cardiovascular disease is the scarcity of *blood dyscrasias.* In this series at least, two of the accepted factors in thrombogenesis, alteration in the blood current and alteration in the vessel wall, outweigh the third factor, alteration in blood content. Of the various leukemias, anemias, purpuras, and Banti's disease, there were only 12 cases among the 648. The incidence of these diseases among all autopsies is considerably higher, inasmuch as the special interest of the hospital in blood dyscrasias is well known throughout the state. Anemia secondary to some other condition was fairly common. No instance of embolism occurred as a consequence of the injection treatment of *hemorrhoids or varicose veins.* Complete thrombosis

of the iliac artery was found in 1 case treated with *thyroid* extract for postoperative hypothyroidism. Several cases of thrombosis were found in diseases of the biliary system, with marked *jaundice* and delayed coagulation time.

Infection of tissues, such as gangrene, abscess, cellulitis, and erysipelas, was present in a majority of surgical cases, in a smaller proportion of medical and miscellaneous cases. Aschoff,[1] reviewing the war-time study of thrombosis made by Dietrich,[7] admitted the very important rôle played by infection in such thrombosis, although he believed that even in war-time thrombosis static factors such as blood loss, debility, bandaging, paralysis often played a part. In this series of peace-time thrombosis, infection ranks far behind stasis.

Cancer was present in almost half of the surgical cases, but in less than one-quarter of the medical cases. Cancer may exert a thrombogenetic influence: 1, indirectly through its general or constitutional effect on the patient—altered resistance, metabolism, debility, secondary anemia, infection, and so forth; 2, through its interference with adequate liver production of heparin; and, 3, directly by its encroachment on vessels; and, 4, dispersal of cancer cells in the blood stream. In several instances cancer cells were seen within the structure of the thrombus. Cancer patients as a rule, however, maintain an elevated metabolic rate, supposedly one of the protective factors against thrombosis.

3. *Wide Range.* Another characteristic of thrombosis is the wide range it traverses, not only with regard to size, numbers, age of patients, and composition, but also with regard to distribution, time of occurrence, clinical manifestations, and most important of all, its effect on the patient. As examples of unusual *composition* in addition to the cancer-containing thrombi mentioned above, the thrombi in 1 case contained within themselves hematopoietic centers, those in another case contained bone. In *distribution*, while found predominantly in certain locations where mechanical factors most handicapped the circulation—the heart chambers, the aorta, the pulmonary arteries, the pelvic veins, and the inguinal arteries and veins—nevertheless thrombi were also found in practically every vessel, large or small, artery or vein.

The findings regarding *time of occurrence* did not always conform to orthodox conceptions: on the 10th to 14th postoperative day following sudden movement, for surgical cases; after weeks or months of recumbency, for medical cases. Among surgical cases, thrombosis and embolism were found to occur anywhere from the time of operation itself to 4 months. One patient had been up and around 4 days when a fatal embolism occurred; another was just entering a cab to go home. Among medical cases, the range ran from the first few minutes following admission, while a history was still being taken, to 1 year. Whereas medical cases on the whole tended to occur later, many of them nevertheless occurred within 1 to 3 weeks

following admission, a period comparable to the orthodox postoperative period among surgical cases.

In more than one-third of the cases, thrombi were located in more than one vessel or organ (for example, femoral vein, adrenal artery and pulmonary artery). In other cases, multiple thrombi were located in the same vessel or organ, particularly the lung. Often these multiple thrombi showed various ages or stages of organization. Hence this series confirms the opinion of Belt,[4] Barnes,[2] and others that thrombosis (and embolism) is most often not a single occurrence but rather a series of occurrences over a period of hours, days or months.

In its effect on the patient, thrombosis extended from a mere incidental postmortem finding through all the stages of morbidity to sudden death. As a cause of sudden postoperative death it has long been recognized, and many efforts have been made to prevent it. As a more frequent cause of morbidity, it has been rather neglected. In this series, for every case in which death was immediately due to thrombosis, there were approximately 3 cases in which it was not. In approximately half of all the surgical cases, thrombosis was a mere incidental finding. No case of thrombosis in the operative site, except dural sinus thrombosis, was of any local consequence, and none was followed by embolism.

The difficulty of classifying patients unequivocably as medical, surgical, traumatic, and so forth, is equalled by the difficulty of classifying thrombosis as simply an incidental finding, as a cause of morbidity, or as a cause of death. This difficulty is frequently encountered in surgical cases dying slowly in coma from pneumonia, hemorrhage, or peritonitis, but with large potentially fatal thrombi, and in medical cases dying suddenly from thrombosis but with potentially fatal cancer, uremia, or peritonitis.

Contradictions. The many contradictions and inconsistencies encountered throughout this series provided a barrier to the formulation of any scheme for the prevention of thrombosis applicable to all cases. Elderly patients with a clinical history of carditis, severe sclerosis, prolonged recumbency, an abdominal operation with subsequent infection and anemia would reveal at postmortem advanced cardiac degeneration, marked pulmonary sclerosis, an aorta covered with atheromatous ulcers throughout its length and down into the femorals—in fact all the supposedly thrombogenic factors, clinical and pathologic—but no thrombus. On the other hand, thrombi have been unexpectedly found in young nonsurgical patients in the apparent absence of most of these factors. While such paradoxical illustrations are fairly commonplace, a number of other inconsistencies and contradictions encountered here warrant brief mention:

1. *Length of Recumbency.* It seemed reasonable to expect that among elderly patients, particularly those with cardiovascular dis-

ease, a prolonged period of recumbency should result in changes conducive to thrombosis. As the number and the hospitalization of elderly patients continue to increase, the study of geriatrics receives wider recognition. Hypostatic pneumonia represents one familiar possibility to be considered in the management of such patients. Recently the effects of prolonged recumbency in elderly persons—at least those effects susceptible of being measured and evaluated—were reported by Laplace and Nicholson.[14] While 10 of their 17 fatalities were laid to recumbency, in no case did it take the form of thrombosis. Nevertheless the effects of recumbency which they considered to be of primary importance, namely, those concerning the blood-vascular system, are the very ones believed to be decidedly thrombogenetic in this series of cases. These include: 1, a sharp decrease in the number and extent of skeletal muscle contractions; 2, decreased voluntary and heart muscle tonus; 3, accumulation of blood in venous capillaries with diminished volume in large vessels; 4, hypostatic congestion in both systemic and pulmonary circulations; 5, a drop in venous and arterial blood pressure. They believed the resultant state of relative circulatory insufficiency to be closely analogous to shock before the stage of vasomotor collapse.

While the changes consequent upon recumbency undoubtedly play an important rôle, what came as a surprise in this series was the briefness of the period of the recumbency. Many medical cases died within the first 3 weeks of hospitalization with its resultant abrupt slowing of all vital activities, a period corresponding to the usual period in postoperative embolism. It would seem that the abruptness of recumbency—with its demand for major adjustments—rather than its duration played the more important rôle. Laplace and Nicholson designated the critical period of recumbency to begin as early as the 2d week and to extend through the 4th week; if the patient survived this period, he had little to fear from additional recumbency.

2. *Nature of Surgical Procedures.* Again it seemed reasonable to expect that subjecting elderly patients to long operations under deep anesthesia with resultant loss of blood and body fluids, drop in pressure and immobility should produce a combination very conducive to thrombosis. Undoubtedly it does. While such combinations did occur, the relatively short and simple nature of many of the operations was unexpected. Because half of them were for cancer, and because a majority of cancer patients arrived here in advanced stages, many of the operations proved to be merely brief explorations with the thrombogenetic factors listed above present in only slight degree. Of the 198 operations, 108 were laparotomies. There were 22 prostatectomies (16 transurethral, 6 suprapubic). Relatively few spinal anesthesias were given. In the majority of cases cyclopropane was used.

3. *Age of Patients.* Whereas the majority of patients were between 40 and 70 years of age, one-seventh of them (91) were under age 30. The thrombi found in these early cases did not represent merely incidental findings; they exhibited the same range from incidental finding to cause of sudden death as did the thrombi in the older cases. Many of them were associated with inflammatory diseases of the heart as the older cases were associated with degenerative diseases. Rheumatic heart disease played an important part. For example, Case 30:132 was a 13-year-old boy hospitalized 2 months with rheumatic heart disease; he died suddenly and unexpectedly while talking to the nurse, with thrombosis of one branch of the pulmonary artery. The youngest case of pulmonary embolism occurred in an infant 8½ months old, Case 35:275, hospitalized only 6 days and exposed to no more hazardous trestment than bilateral myringotomy.

Because of its contradictory and deceptive clinical behavior, accurate diagnoses at times proved very difficult or even impossible. The fact that major pulmonary thrombosis may form during a state of coma from some other condition such as peritonitis or uremia, and so mask or fail to provoke any sudden clinical episode, indicates one type of difficulty. Another familiar type is illustrated by the following 2 cases: Case 37:136 was a woman aged 61 who died suddenly following movement on the 19th day after cholecystectomy. Though clinically it appeared to be typical pulmonary embolism, none was found at autopsy; the death was cardiac. Case 36:101 was a man being treated conservatively for gall bladder disease; on his 16th day of recumbency he turned on his side and suddenly died. At autopsy, while other lesions were also present, there was a gross pulmonary thrombosis.

It is not essential for the consideration of thrombosis as primarily a medical problem to present a detailed description of all its principal types. They nearly all lend support to this consideration. However, as they do so in slightly different fashion, a brief description will be given of four of them—pulmonary, cardiac, coronary, and inguinal.

Pulmonary Thrombi (and Emboli).—It can be seen from Table 2 that both in frequency of occurrence and in seriousness of effect pulmonary thrombi (and emboli) rank first in this series, far ahead of coronary and cerebral thrombi, the other potentially fatal types most frequently found. Barnes[2] in a recent article on pulmonary emboli estimated that over 3,000,000 persons now living in the United States would ultimately die of this condition, and he regretted the failure of vital statistics to indicate its true magnitude. Jackson[13] believes that many acute attacks now being diagnosed as coronary thrombosis are not coronary thrombosis at all, but actually thrombosis (or embolism) of the pulmonary artery. This series of cases tends to substantiate the conclusions of both men. A striking illus-

tration can be provided by Case 37:300: this woman, aged 62, a cardiac patient without previous hospitalization, suddenly dropped dead in a few minutes after admission, while a brief history was being taken preparatory to assigning her to the proper service. Postmortem disclosed a massive fresh bilateral pulmonary thrombus.

The above case also may be used in directing attention toward two of the prominent traits of pulmonary thrombosis in this series: 1, its tendency to occur more often among strictly medical patients; and, 2, the brief period of hospitalization (or recumbency), if any, necessary for its formation in medical cases. As shown in Table 2, two-thirds of this group were strictly medical patients. Many of the ordinary medical cases occurred within 1 to 4 weeks of admission, the critical period of recumbency in the development of this condition.

TABLE 2.—PULMONARY THROMBOSIS AND EMBOLISM.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
Number of cases:	226.	98.	17.	341.
Size:				
Gross	142	64	14	220
Microscopic	84	34	3	121
Alone, or with other thrombi:				
Alone	125	61	9	195
With cardiac thrombi	49	7	..	56
With coronary thrombi	10	1	..	11
With inguinal thrombi	21	7	4	32
With any other thrombi	69	30	4	103
Associated diseases:				
Cardiac: primary	106	2	..	108
secondary	61	55	8	124
Cancer	58	53	1	112
Effect:				
Incidental finding only	57	29	3	89
Contributory	80	38	10	128
Fatal: with sudden death	50	18	3	71
without sudden death	39	13	1	53

Table 2 brings out the preponderance of cardiac patients among the medical cases. In almost half of the medical cases it was the primary ailment, and in half of the remainder it was an important secondary ailment; 49 medical cases also showed cardiac (mural) thrombi, and 10 coronary thrombi. Unfortunately, no tabulation was made of cases showing marked coronary disease or occlusion without actual thrombi; otherwise the close relationship would have been more evident.

The only other condition occurring often enough to warrant inclusion in Table 2 was cancer. Among the 31 surgical cases where death was directly attributable to thrombosis (or embolism), cancer was present in 16 cases. Non-cardiac, non-cancer cases accordingly occurred only rarely.

Two additional characteristics of these thrombi deserve mention. *First*, non-fatal pulmonary thrombosis, with or without clinical or pathologic significance, outnumbers (217 to 124) the fatal form, and

indicates its numerically greater rôle in causing morbidity of various degrees instead of immediate death. As only actually demonstrated thrombi were used in this series as a basis for the statistics, cases with pulmonary infarct but no discernible thrombus were not included; otherwise its rôle in morbidity would assume greater proportion. *Second*, among cases where differentiation could be made with assurance, pulmonary thrombosis outnumbered pulmonary embolism particularly in the non-fatal cases.

Cardiac Thrombi.—In numbers, if not in fatal potentialities, uninfected cardiac or mural thrombi of various forms came second, as shown in Table 3. To the belief that thrombosis is primarily a medical problem, two features in particular lend support: 1, the large proportion (117 out of 140) of strictly medical cases; and, 2, the even larger proportion of patients (126 out of 140) with primary or secondary heart disease of one type or another. The comparatively few cases of cancer are striking in view of its much larger proportion in the other groups.

Certain of the findings in this group duplicated findings by Harvey and Levine[9] in a study of Boston autopsies between 1913 and 1929. They found 111 uninfected thrombi among 2091 posts, an incidence of 5.3%; here 140 were found, an incidence of 5.4%. In their series 66% were males; here 58%. In both series, the four chambers were involved in the same order of frequency: right auricle, left ventricle, left auricle, right ventricle; the auricular appendages and the ventricular apices were the commonest sites. They concluded that ventricular damage (infarction) subsequent to coronary disease, particularly occlusion, and stasis from improper functioning of the auricles, particularly fibrillation, were the two most frequent mechanisms for the formation of cardiac thrombi. Myocardial fibrosis appeared as a very common underlying condition in this series. While the majority of cases in both series occurred after age 40, where degenerative heart disease prevails, in our series 14 cases occurred before age 30, 7 of them with rheumatic heart disease. Among the entire group of 140 cases, the ages ranged from 11 months to 97 years.

The effect of mural thrombosis on the patient has not been included in Table 3 because it proved too difficult to evaluate with reasonable assurance, mural thrombi frequently forming only one link in a chain of lesions. To separate their individual effect from the total effect is practically impossible. While fatal cases have been reported, in no instance in this series was mural thrombosis regarded as the immediate cause of death. Undoubtedly it provided the origin of several instances of fatal embolism elsewhere.

Coronary Thrombi (see Table 4). It seems superfluous to use coronary thrombosis in support of a conception of thrombosis as a medical problem, since it occurs predominantly among medical (cardiac) patients. Whereas recognition and understanding of the

nature of thrombosis in general have been due largely to pathologists (beginning with Virchow[22] in 1846–56 and including Welch[24] and Aschoff[1]), recognition and interest in coronary thromboses have been due almost solely to clinicians (beginning with Herrick[11] in

TABLE 3.—CARDIAC (MURAL) THROMBOSIS.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
Number of cases:	117.	23.	0.	140.
Sex:				
Male	81	16	..	97
Female	36	7	..	43
Size:				
Gross	103	18	..	121
Microscopic	14	5	..	19
Number of chambers involved:				
Single	78	19	..	97
Multiple	39	4	..	43
Alone or with other thrombi:				
Alone	38	10	..	48
With pulmonary thrombi	49	7	..	56
With coronary thrombi	13	3	..	16
With inguinal thrombi	5	3	..	8
With any other thrombi	32	7	..	39
Associated diseases:				
Cardiac: primary	90	5	..	95
secondary	18	13	..	31
Cancer	7	5	..	12

TABLE 4.—CORONARY THROMBOSIS.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
Number of cases:	34.	6.	0.	40.
Sex:				
Male	28	6	..	34
Female	6	0	..	6
Size:				
Gross	16	2	..	18
Microscopic	18	4	..	22
Associated lesions:				
Infarct	20	4	..	24
Cardiac thrombus	13	3	..	16
Pericarditis	14	2	..	16
Rupture	2	..	..	2
Aneurysm	4	1	..	5
Pulmonary thrombus	10	1	..	11
Other thrombus	11	..	..	11
Number of episodes:				
None	17	3	..	20
Single	2	2	..	4
Multiple	15	1	..	16
Effect:				
Incidental finding only	12	2	..	14
Contributory	14	3	..	17
Fatal with sudden death	8	1	..	9

1912 and including Riesman,[21] Levine,[15] Middleton,[17] and Willius.[26] By its nature and location it combines elements both of heart disease and of thrombosis. It is accountable directly and indirectly for a multitude of lesions in both categories. Case 37:49 furnished a concrete illustration of the wide extent of its accountability: This

man, aged 55, gave a history of coronary attacks over a period of 26 months. He died 12 days following admission. At postmortem there were found a large, fairly recent thrombus occluding the anterior descending branch of the left coronary, an older calcified thrombus in one of its larger branches, and microscopic thrombi in numerous small branches; mural thrombi of various ages in three chambers; multiple areas of old and recent myocardial infarction; impacted emboli in the pulmonary arteries, with smaller propagating thrombi beyond them and with multiple areas of old and recent pulmonary infarction.

Among the common heart lesions found at autopsy, coronary thrombosis ranked eighth, far behind chronic fibrous myocarditis and coronary sclerosis. Heart lesions among the 2613 postmortems occurred very frequently, reflecting the constantly large proportion of heart patients among the hospital population. However, the majority of such patients were of the rheumatic, chronic degenerative, or congestive heart failure type, more conducive to mural or pulmonary thrombosis, and not of the anginal type, more related to coronary thrombosis. Like cerebral thrombosis, it frequently occurs as a primary ailment, during activity, outside the hospital, and may not result in hospitalization. Mural and pulmonary thromboses in this series were shown to occur as secondary complications following hospitalization or recumbency. Like hypostatic pneumonia, they represent hazards of hospitalization; they are the results of recumbency. Coronary thrombosis, on the other hand, is a cause of recumbency. In severity of effect, it produced only 9 fatalities compared with the 78 fatalities produced by massive pulmonary thrombosis or embolism. This lends support to the belief of Jackson[13] and others that many attacks diagnosed as coronary thrombosis without autopsy confirmation are in reality examples of pulmonary thrombosis.

Among the principal types of thrombosis, coronary thrombosis ranked sixth, and might have fallen to seventh had there been more brain examinations. It must be stated, however, that only actual thrombi, in the exact pathologic meaning of that term, were included. Occlusion produced by methods other than thrombosis (sclerosis and possibly spasm) were excluded, as were cases of myocardial infarction (two to three times as frequent as thrombosis) wherein no thrombus was found. Half of the cases were merely of microscopic size. Yet microscopic thrombi in this organ are as important as in the brain, since Blumgart[5] has recently demonstrated the damaging effects of anoxia in heart muscle of only a few minutes' duration.

Apart from its low incidence, a number of miscellaneous findings might be mentioned for their general interest. *Sex:* males outnumbered females 5 to 1. This ratio was obtained also in another disease in this series of 2613 postmortems, namely cancer of the

lung, wherein the culpability of tobacco has also been raised. In White's[25] series of 21 clinical cases of coronary thrombosis under age 40, all used tobacco. *Age:* although the majority of cases fell between the ages of 50 and 70, there were 4 young cases (ages 8, 14, 17 and 25), all of whom showed rheumatic stigmata. *Occupation:* that coronary thrombosis is not confined to a wealthy, white-collared, worried clientele, such as have furnished the material in the reports of numerous clinicians, is shown by the occupations and financial status of the patients comprising this series. Most of them were farmers or laborers with only 3 non-manual workers among the males. Of the 40, 37 were ward patients. *Surgical cases:* though it was necessary to classify 6 cases as surgical, all of them were actually cardiac patients with a superimposed surgical emergency, such as acute appendicitis or acute urinary retention. *Canalization:* 5 cases showed restoration of flow through recanalization, a method somewhat neglected or forgotten in the search for adequate collateral flow.

TABLE 5.—INGUINAL (ILEO-FEMORAL) THROMBOSIS.

	Medical cases.	Surgical cases.	Miscellaneous cases.	Total cases.
Number of cases:	33.	13.	6.	52.
Vessel:				
Artery	7	1	..	8
Vein	24	11	6	41
Both	2	1	..	3
Side:				
Right	12	4	1	17
Left	12	8	3	23
Both	9	1	2	12
Number infected	15	8	2	25
Associated diseases:				
Cardiac: primary	9	..	..	9
secondary	14	8	3	25
Cancer	14	11	1	26
Effect:				
Incidental finding only	11	8	2	21
Contributory	16	2	1	19
With fatal embolism	6	3	3	12

Inguinal Thrombi (see Table 5). Thrombi in these vessels (ileo-femoral arteries and veins) were found less frequently than thrombi in the pelvic veins (74 cases) or in the aorta (56 cases). There were 52 cases divided almost evenly as to sex, with 27 males and 25 females. The inguinal region, embracing both iliac and femoral, is one wherein structural or mechanical handicaps combine under certain provocations to exert a powerful thrombogenetic influence. Any list of such handicaps would naturally include the following: the compression of both artery and vein under Poupart's ligament; compression of the iliac vein under the artery; compression from regional abnormalities (in this series enlarged lymph nodes due to infection, cancer, metastases, aleukemia, abscess, and dissecting hematoma); abdominal or pelvic distention from fluid or gas; the venous valves; the entering angle of contributory veins; supine

position in bed with failure to relax groin by bending knee; immobility, venous stasis, decreased muscle and vessel tonus, distance from the heart. Like the pelvic veins, these vessels lie close to the divide between the portal vein drainage and the vena cava drainage, and consequently are susceptible to the effects, if any, of a reflux of portal blood into the systemic veins (Havlicek's[10] theory of thrombogenesis). The comparative freedom of the axillary region from such handicaps is indicated by the presence of only 5 cases with thrombosis in that region, all apparently provoked by some unusual impediment to venous return (cancer of lung, axillary metastases, large pleural effusions).

This region, accordingly, in the size and importance of its vessels, and in its vulnerability to a multitude of structural handicaps, appears to offer an ideal site for the formation of dangerous thrombi whenever the imposition of an additional hazard, as an operation, a fracture, or a birth, activates these potential handicaps. Yet, as Table 5 shows, such additional provocation need not be required: a majority of these thrombi were found in medical patients subjected only to recumbency.

Ten of the patients placed correctly in the medical group illustrate nevertheless how easily and erroneously at times surgery can be held accountable for the thrombus. Seven of them had cancers thought to be too far advanced for surgery, 2 had cancers being treated with Roentgen ray instead of surgery, and 1 had a goiter, causing too great a risk for surgery. Similar cases, though with thrombi in different sites, were encountered wherein surgery was not undertaken because of the advanced state of the disease (generally cancer), the poor risk, or because other treatment was substituted. Other cases were encountered wherein surgery had been postponed, supposedly merely temporarily, because of elevated temperature, sore throat, or irrelevant personal reasons. Yet in all these cases, had the desired or contemplated surgery taken place, it would ordinarily have been held accountable for the thrombosis found at postmortem; it would have been necessarily classified as a surgical case in this series.

Among the medical cases the period of recumbency frequently lasted less than 3 weeks. Among the surgical cases the postoperative period of recumbency never was longer than 19 days, and generally was 11 to 14 days. However, 1 case dying on the day of operation for brain tumor, with a large incidental inguinal thrombosis at postmortem, brings out the need of considering the preoperative period also. Case 34:197 indicates that even recumbency is not required when underlying factors are sufficiently strong: in this patient, a man of 48, the thrombus first made itself manifest very abruptly while he was bent over in a field picking cucumbers; the process had been set in motion by a metastasis from an unsuspected cancer of the rectum. Among fracture cases on the ortho-

pedic service, customarily subjected to the longest periods of recumbency and immobility, only 4 cases of inguinal thrombosis were found.

Summarizing the rather inconsistent influence of recumbency in this area, it was found that 1, inguinal thrombosis occurred most often among strictly medical cases; 2, it occurred rarely among fracture cases subjected to the longest periods of recumbency; and 3, it occurred frequently within a comparatively short time, seemingly instigated more by the shock and abruptness of recumbency than its prolongation.

The potentialities of large inguinal thrombi in cases where death was due to other causes can best be indicated by citing a typical instance: Case 33:248 was a 65-year-old male who died of cancer and heart disease 30 days following the application of a double hip spica (fracture due to cancer metastases). At postmortem, the left ileo-femoral vein was completely thrombosed from a point too far below Poupart's ligament to be reached by probing up to the origin of the inferior vena cava. There had been no swelling of the leg, no clinical manifestation and no embolus. It was merely an incidental postmortem finding.

Altogether 13 such cases were found of large potentially dangerous inguinal thrombosis. They make one wonder what would happen if the patient had not died of an intervening pneumonia, uremia, peritonitis, cancer, or heart disease. They make evaluation of the effect of these thrombi difficult and raise objection against classifying them as merely incidental findings. Though all of the inguinal thrombi were large, one extending from the level of the renal artery to the popliteal fossa, only 12 of them gave rise to fatal embolism.

Discussion. Virchow[22] between 1846 and 1856 evolved a conception of thrombosis, largely mechanical, that is accepted today. He declared the process to be dependent upon three conditions: 1, alteration (slowing) of the blood current; 2, alteration (damage generally from infection or degeneration) in the vessel wall; 3, alteration (chemical and physical) in the blood content. Since his time other students of the problem have furnished additional details or refinements of these three fundamental conditions. Zahn[27] called attention not only to the architecture of a thrombus, but to the necessity for a flowing stream; von Recklinghausen[20] to the whirling or eddying current. Welch[24] repeated many of the earlier experiments, particularly those of Eberth and Schimmelbusch,[8] emphasizing the combination of a slowed circulation and a damaged intima. Howell[12] added heparin, a constituent of the blood formed in the liver. Dietrich,[7] studying war-time thrombi, emphasized infection. Aschoff,[1] studying peace-time thrombi, emphasized stasis. Havlicek[10] believes a reflux of toxin-laden blood from the portal system into the caval system leads to agglutination and thrombosis. Peterson[19] believes the weather exerts a marked thrombogenetic influence; that certain meteorologic pressor episodes produce a fall in

blood pressure, a sticky endothelium, an increase in fibrinogen, and a relatively acid organic status. Murray and Best[18] and their co-workers are currently administering refined and concentrated heparin to human beings and determining what protection it affords following extensive surgical procedures.

The cases in this series are indicative not only of the increased incidence of thrombosis which has taken place largely since the World War, but also of its preponderance among strictly medical patients and of its more frequent rôle as a cause of morbidity than of death. Its increase has been attributed to a number of circumstances, particularly: 1, lengthening of the average life expectancy; 2, consequent increase in number and longer survival of cardiac patients; 3, increase in the hospitalization of patients, and in general, earlier and more widespread resort to recumbency, to the practice of "going to bed," with less provocation than in hardier days; 4, larger volume of surgery; 5, greater use, especially among the Germans, of intravenous therapy and diuretics. Thrombosis should be placed besides pneumonia as one of the hazards of hospitalization. Of the 648 cases in this series, with the exception of 11 coronary cases, only 7 entered here because of thrombosis.

Analysis of the individual cases in this series indicates that thrombosis is a product of variables. In any 2 patients with thrombosis the factors entering into the process may vary widely in number, in individual potency, and in the manner in which they are combined. Again, in 2 patients of the same age and sex, with practically identical alterations in two of the fundamental conditions—for example, vessel wall (atheromata) and blood current (stasis)—with the same primary disease, and subjected to the same medical management, thrombosis may develop in one but not in the other. The antithrombotic (heparin?) composition of the blood content—the third fundamental—has been sufficient to provide protection in one case, but not in the other. It is a matter of degree as well as number of factors. Such variability increases the difficulty of developing any formula for prevention which could be applied in all cases.

This series emphasizes the importance of the underlying or dormant medical factors, not only among the medical patients but also among the surgical, obstetric and traumatic patients. When such factors are present in adequate degree the shock of a superimposed operation, fracture, or childbirth, is not essential. Abrupt recumbency for a period of only a few days or weeks is capable of setting the dormant thrombogenetic factors into motion.

Among medical factors, a decompensated cardiac condition overshadows all others. Cardiac patients of the anginal type, without decompensation, are prone to develop coronary thrombosis. To them recumbency is no hazard. Cardiac patients without angina, but with decompensation, are prone to develop other forms of thrombosis—mural, pulmonary, inguinal, and pelvic. To them

recumbency is a hazard. They need not be elderly patients with progressive degeneration of the cardiovascular equipment, although such patients constituted the majority here. They may be young patients generally with rheumatic or bacterial inflammation. It is the condition of decompensation, not whether its cause is degeneration or inflammation, nor the age of the patient, which is important.

Prevention. Many practical measures to prevent thrombosis have been recommended, mainly by surgeons attempting to avoid postoperative embolism. For a list of such measures and a discussion of their merits, two recent publications are helpful: An article on Pulmonary Embolism, by Arlie Barnes,[2] and a chapter on Thrombosis, by John Homans.[16] According to Homans, most measures are aimed at three objectives: to keep the fluid content normal, to prevent a rise in intraäbdominal pressure, and to invigorate the venous return from the legs. He believes that if everyone confined to bed under conditions which threaten thrombosis could live with the foot of the bed elevated and could be protected from increased intraäbdominal pressure, thrombosis and embolism would never occur (granting at the same time the limited application of such methods because of other dangers).

Thrombosis, however, does not arise from any single cause, and there is no specific preventive. Being a product of variables, no constant formula for prevention can be laid down. In this series, it appears most frequently as the consequence of a chain of dormant medical factors (such as an impaired heart plus a local handicap plus deficient anticoagulant quality of blood) activated by the imposition of some shock (operation, trauma, pregnancy, recumbency). The links in the chain varied widely in number and in individual potency. The predominant medical factor, however, was an impaired heart (regardless of age), and the predominant activating shock was simple recumbency among strictly medical patients. Consequently, whatever additional measures of prevention may be suggested by this series, they apply to these two conditions.

1. *Impaired Heart.* Inasmuch as thrombosis is an abnormality of the vascular system (heart, vessels, blood), maintenance or restoration of the normal structure and functioning of this system is the chief objective. Avoidance of, or protection against, outside interference with its normal function must likewise be included. Typical illustration of outside interference is furnished by encroaching tumors, by compression under Poupart's ligament, by the pressure of large volumes of fluid in the abdominal or pleural cavities. Cardiac competency is the greatest single defense against thrombosis, and its lack the greatest single danger. Decompensation—for reasons obviously more serious than the possibility of thrombosis—should be corrected wherever possible. In so doing many conditions conducive to thrombosis, which may exist independently, however, as well as secondary to decompensation, will be overcome.

Typical illustration of such conditions is furnished by congestion or stasis in either the pulmonic or the systemic circulation (leg and pelvis particularly), by auricular fibrillation, by reduction of fluid within the vascular system (dehydration), by enfeebled blood current.

2. *Recumbency.* Under certain circumstances the benefits of recumbency are also accompanied by a certain degree of risk or hazard. The circumstances have to do chiefly with cardiac impairment, regardless of age, with or without decompensation, but excluding the anginal type. The risks include: 1, a condition of general circulatory deterioration described by Laplace and Nicholson[14] as analogous to shock; 2, hypostatic bronchopneumonia, and, 3, thrombosis. They arise apparently from the abruptness of the change, as the critical period is relatively short, covering only the first 2 or 3 weeks. They can be reduced by any measures undertaken to make the transition to a complete bedridden status a gradual rather than a sudden process, both in time and in methods. These measures must be varied according to the nature and degree of the patient's illness, but in general as much mobility of the patient should be retained or provided as is compatible with his condition.

A certain amount of regular or daily mobility provides the best single protection against the risks of recumbency. Homans, advocating short confinements after abdominal operations, believes convalescence is shortened and vigor more quickly regained when the patient has been made to get out of bed very early, if only for a few minutes daily. For strictly medical patients the risks of recumbency are reduced in proportion to the degree of mobility retained during the relatively short critical period of transition to a bedridden status.

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CORONARY THROMBOSIS AMONG WOMEN.

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Little doubt exists that coronary thrombosis occurs more frequently today than ever before, and numerous opinions have been expressed in explanation of this phenomenon. Prominent among them is the assertion that a better and more widespread understanding of the disease has greatly increased the accuracy of diagnosis and that the increased incidence, therefore, is apparent rather than real. It is true that the medical profession at large has improved the accuracy of diagnosis but this fact does not wholly satisfy the presumption that the incidence of coronary thrombosis has not increased, as careful analyses of postmortem material of two decades ago reveal relatively few cases of coronary thrombosis as compared to the cases that are observed today.

Another frequently aired opinion emphasizes the influence of the stresses and strains of modern life, the worries contingent on financial catastrophies and the ever-increasing uncertainties prevailing in the business world of today. There seems to be little doubt that these stresses are participating factors, but again the question is not completely answered.

Likewise, the influences of heredity have been mentioned as noteworthy factors in the increasing incidence of coronary thrombosis. This belief has been based on the assumption that the United States has reached the age where the adverse influences of heredity, so far as the cardiovascular system is concerned, are becoming evident owing to the conspiring influences of the modern environment. While the influences of heredity cannot be denied, the data on the subject are so inadequate that this thesis cannot be established as a fact.

The solution of the problem seems to depend on the solution of the cause or causes of atherosclerosis, and it appears at this time that the answer may be supplied through the medium of biochemistry.

The reasons for our interest in the subject of coronary thrombosis among women are dependent largely on certain data disclosed in a previous investigation by one of us.[3] This study, which comprised 370 cases of coronary thrombosis, was based only on the selection of cases in which complete data were available. It disclosed that

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there was a great discrepancy in the incidence according to sex. There was a marked predominance among men; the ratio of men to women was 7 to 1. Furthermore, it was shown that coronary thrombosis occurred considerably later in life among women than it did among men; in fact, it occurred on an average of 6 years later among women. It, therefore, seemed desirable to study carefully a larger group of women who had coronary thrombosis, in order to determine, if possible, any other striking differences in the manifestations of the disease in the two sexes.

Levy and Boas[2] recently reported a study of 169 women who had coronary disease. Their patients were not selected exclusively on the basis of coronary thrombosis but on criteria that warranted the diagnosis of coronary disease. Their conclusions, which are substantiated only in part by this study, included the following deductions: 1, Coronary disease is more common among men than among women, and in all but 7.7% of the cases either hypertension or diabetes mellitus occurred; and, 2, coronary disease occurs infrequently among women under the age of 50, unless it is associated with hypertension or diabetes mellitus.

Material. One hundred consecutive women who had coronary thrombosis form the basis for this study. In 35 cases the occlusion occurred while the patients were under observation at The Mayo Clinic. Sixteen patients were observed within a month following the occlusion, 24 within 6 months, 7 within a year, 7 within 18 months and 7 after 2 years or more. In 4 cases, it was impossible to determine accurately the time that coronary thrombosis occurred. In cases in which the patients were not observed during the time of acute coronary closure, characteristic histories, typical electrocardiographic findings or demonstration of the infarct at necropsy were convincing evidence of its occurrence.

Age Incidence. Only 8 patients were less than 50 years of age at the time the thrombosis occurred; 2 were in the fourth and 6 were in the fifth decades of life respectively. The youngest patient was aged 30, the oldest 85, and the average age for the group was 63. The average age for males in the previous study[3] was 57.3 years. Eighty-nine per cent of the patients were in the sixth, seventh or eighth decade of life, while in the previous study 79% of the men were in the same age periods. Three women were between the ages of 80 and 89. These data clearly demonstrate the tendency for coronary thrombosis to occur later in life among women than among men.

Mortality. In 54 cases the patients were dead at the conclusion of this study and in all but 9 of these cases death was directly attributable to the heart. In 32 cases death occurred soon after coronary occlusion and in 13 cases later, as a result of ensuing congestive heart failure. In 4 cases the cause of death could not be determined; in 5 cases death resulted from diseases entirely unrelated to the heart. Forty-six patients were living at the conclusion of the study.

Recurrent Coronary Thrombosis. Seven patients suffered from recurrent coronary thrombosis. This incidence is considerably less than that noted in the previous study, which comprised both men and women. In that study, the incidence of recurrent episodes was found to be 19.7%.

In 6 cases, 2 attacks of coronary thrombosis occurred and 1 patient

survived 3 attacks. This patient is living and well, 7½ years following the first occlusive episode and 4 years following the third; she is now 73 years of age. The intervals between the attacks ranged from 2 months to 7½ years.

Another patient, who had 2 attacks of coronary thrombosis, is living and well. She is now 83 and had the last attack 4 months before this article was written. These 2 patients emphasize the remarkable tolerance and reparative powers of the heart to such severe disease which is observed from time to time even among aged persons.

Evidences of Heart Disease Preceding Coronary Thrombosis. In 78 cases subjective evidence of heart disease occurred before the onset of coronary thrombosis. The symptoms had been present from 2 months to 15 years. The most common symptom was dyspnea which was associated with accustomed effort; this occurred in 65 cases. The anginal syndrome occurred in 27 cases. Thirteen patients had had one episode of congestive heart failure; hypertensive heart disease was coëxistent in every case in which congestive heart failure had occurred. Some overlapping of these symptoms obviously occurred. It is interesting and significant that only 22 patients experienced their first conclusive cardiac symptoms with the onset of coronary thrombosis.

Associated Conditions. We were greatly interested in the report of Levy and Boas, in which they said that hypertension and diabetes mellitus occurred in 92.3% of the cases. This incidence was considerably out of line with our clinical impressions.

In our series 66 patients were known to have had hypertension before the onset of coronary thrombosis and it is probable that the incidence actually was somewhat higher, owing to the fact that blood pressure at times fails to attain its former level after an attack of coronary occlusion.

Data regarding diabetes mellitus were available in all but 12 cases; in these cases death occurred very soon after the occlusive attack and before laboratory studies could be carried out. Only 11 patients had diabetes mellitus. It is, of course, true that the degree of atherosclerosis frequently is marked among diabetic patients and that coronary disease among them is common. Variations in the results of different groups of clinical material obviously occur and it, therefore, is important not to accord too much importance to certain incidental findings.

In 77 cases the ratios of height and weight were available; in 87% of these cases there were varying and definite degrees of obesity. In a previous publication, Goldsmith and Willius[1] presented data obtained in 300 cases of coronary thrombosis; these data showed that a tendency to overweight occurred among patients of all ages with the exception of men who were over 70. There seems to be no doubt that obesity is a very undesirable status in heart disease and of itself is capable of swinging the balance from cardiac competence to incompetence.

The rather frequent association of cholecystic disease and coronary disease has received considerable attention, and the association of cholecystic disease and obesity also has been noted. In this study 16 patients had proven disease of the gall bladder. Nine patients had been operated on elsewhere, prior to the onset of coronary thrombosis; 2 were operated on after recovery, and in the remaining 5 cases, cholecystographic study clearly revealed the condition.

The occurrence of other diseases, such as carcinoma, hyperthyroidism, syphilis, and so on was purely casual and merits only mention.

Situation of Infarcts. In 86 cases the situation of the infarct was determined by electrocardiographic study or by postmortem examination. In the remaining cases death occurred before electrocardiographic examination was possible, or else necropsy was not permitted. It is interesting to note

that in all necropsied cases in which the electrocardiographic prediction of the situation of the infarct was made the predictions were proved to be correct.

The infarcts involved the anterior portion of the left ventricle in 30 cases, the posterior portion in 50 cases, and both anterior and posterior portions in 6 cases (recent and old infarcts). These figures are different from those of the previous study,[3] in which the anterior surface of the left ventricle was involved in 56.3% of cases and the posterior wall in 43.6%. We do not believe that these differences are significant, but feel that they represent only the differences that may be anticipated in the study and comparison of different groups of cases.

Duration of Life in Cases in Which Coronary Thrombosis Proved Fatal. In 45 cases, as previously stated, death was directly attributable to coronary thrombosis or its sequelæ. Nine patients lived less than 24 hours following the onset of the occlusive episode. Six patients lived less than a week, 8 less than a month and 9 less than 6 months. Six patients lived less than a year, 4 lived less than 2 years and only 3 lived more than 2 years. The average duration of life in cases in which the patients died of heart disease was 11 months.

Duration of Life in Cases in Which Coronary Thrombosis Did Not Prove Fatal. Information was available regarding the state of health of 43 patients. Three patients could not be traced. Twenty-eight patients were alive within a period of 5 years following coronary thrombosis, 12 were alive within a period of 5 to 10 years and 3 lived more than 10 years.

Eighteen patients reported their state of health as good, 5 said that they were well with the exception of occasional anginal seizures, 14 were only in fair health and 6 were in very poor health. The latter include patients who had severe recurrent anginal seizures, severe dyspnea, congestive heart failure or a cerebral vascular accident.

Summary. Only two striking differences were noted in coronary thrombosis among women, as compared with men. The first is its relative infrequency among women; the ratio of men to women approximates 7 to 1. The second striking difference is the tendency for the disease to occur later in life among women; the average age of women was 6 years greater than the average age of the men. The relatively late appearance in life is presented more vividly if one recalls the fact that, in this series of cases, coronary thrombosis was recorded in 89% of the cases in which women were between the ages of 50 and 80 years and in 79% of cases in which men were of the same age. It therefore appears justifiable to assume that women are less susceptible to the development of coronary thrombosis than are men, and that when it occurs among women, it tends to occur later in life.

The association of hypertension, diabetes mellitus, and other conditions appears only to bear a relationship compatible with the predominant age periods represented by the group of patients included in this study.

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STUDIES ON THE CIRCULATION IN PREGNANCY.

V. LEAD 5 OF THE ELECTROCARDIOGRAM IN PREGNANCY, INCLUDING NORMAL, CARDIAC AND TOXEMIC WOMEN.

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REPORTS of the use of the chest lead of the electrocardiogram in general clinical medicine,[7,11] led us to study it in pregnancy. The study was intended primarily to ascertain what Lead 5* (anterior chest—left leg) would show throughout the course of normal pregnancy; in addition, its possible usefulness in cardiacs and toxemics was investigated.

Studies of the conventional leads of the electrocardiogram in pregnancy in this clinic have showed a tendency towards left axis deviation as pregnancy progresses with a shift back towards normal in the final weeks.[2] Also it was further showed[3] that the Q–3 is deep, according to Pardee's criteria[8] in 5% of cases. In this investigation, it was planned to discover whether there were changes in Lead 5 of the electrocardiogram which correlated with changes in the conventional leads.

Procedure. There were 398 electrocardiograms taken on 288 pregnant women at the Boston Lying-in Hospital. In some patients single observations were made. In many, both antepartum and postpartum observations were made. In a few cases monthly electrocardiograms were taken throughout pregnancy. The patients were divided into three groups, 1, those with normal hearts (104 cases); 2, those with heart disease (140 cases; 111 rheumatic heart disease, 13 congenital heart disease, 16 hypertensive heart disease); and, 3, those with the "hypertensive-toxemia" syndrome, *i. e.*, patients with pre-eclamptic toxemia or essential hypertension without heart disease (39 cases). There were also 5 patients with miscellaneous conditions.

* At the time this study was initiated the optimum position for placing the chest electrode had not been agreed upon; therefore the position chosen for applying the chest electrode in this study was that approximating Lead 5 as described by Wood *et al.*[11] This position seemed best suited for the study of pregnant women, as will be pointed out below. The placing of the electrode as described above compares most closely with Lead CF4 as recommended by the American Heart Association and the Cardiac Society of Great Britain and Ireland. It is emphasized that in this study the electrodes were connected in such a way that positivity is represented by downstrokes and negativity by upstrokes; hence the T waves were normally inverted.

Methods. The electrocardiograms were taken with a Boulitte machine. German silver electrodes were used and contact between skin and electrode was made by a paste described by Jenks and Graybiel[6] containing sodium chloride, pumice, gum tragacanth, potassium bitartrate, glycerine, carbolic acid, and water.

The exploring electrode was placed in the fourth interspace 5 cm. to the left of the mid-sternal line. The large breasts of the pregnant women make unfeasible placing the electrode over the apex. The indifferent electrode was placed on the left leg. The patient was in a sitting position.

In addition, later in the study, Lead 5 was determined with the patient in deep inspiration and full expiration. Conventional leads were taken in all cases in the usual manner.

Physical examination of the heart and lungs was made in all cases and in many 7-foot Roentgen-ray photographs and circulatory studies were done, the details of which have been previously published.[4]

In examining the tracings, deviations from the more usual type of normal Lead 5 were noted. These comprised the following: an absent *Q*–5 or one less than 2 mm. amplitude, a monophasic *QRS*, notching or slurring of *QRS*, abnormalities of *RS–T* segment, flat, diphasic or upright *T*–5. Changes in *Q*–5, *RS–T* segment or *T*–5 were considered of special interest since in non-pregnant individuals they may indicate myocardial disease.

TABLE 1.—OBSERVATIONS ON LEAD 5 OF THE ELECTROCARDIOGRAM IN 288 PREGNANT WOMEN.

	Type of patient: Number of patients:	Normal 104	Cardiac 140	"Toxemic" 39	Misc. 5	Total 288
T–5	Flat	4	7	0	0	11
	Diphasic	10	30	0	0	40
	Upright	8	20	10	1	39
	Variable	3	0	1	0	4
QRS	Notching or slurring	5	39	8	0	52
	W or M shaped	1	2	0	0	3
	Q–5 less than 2 mm.	0	18	4	0	22
	Q–5 absent	0	5	1	0	6
RS–T	(Above (+) or below (−) isoelectric line):					
	>1 mm.+	0	3	0	1	4
	>2 mm.−	0	4	0	0	4
Q–3	Deep	5	5	1	0	11
Left axis deviation		42	38	14	1	95

TABLE 2.—INCIDENCE OF UPRIGHT *T*–5 IN PREGNANT WOMEN.

Normal pregnant women	8 in 104— 7.7%
Rheumatic heart disease	10 in 111— 9.0%*
Congenital heart disease	1 in 13 —15.4%*
Hypertensive disease—toxemia	8 in 55 —14.5%*
"Toxemia" alone	4 in 39 —10.2%
Miscellaneous	1 in 5 — %

* All patients receiving digitalis excluded.

Results. The findings in this study are presented in Table 1. It will be noted that slurring and notching of *QRS*–5 is quite common.

T-wave variations, it will be seen, were not infrequent. Flat and diphasic *T* waves occurred in 51 patients—that is, in approximately one-sixth. An upright *T*–5 was observed 39 times, 8 times in normal patients, 20 times in cardiacs and 10 times in toxemics and once in the miscellaneous group. Table 2 shows this in tabular

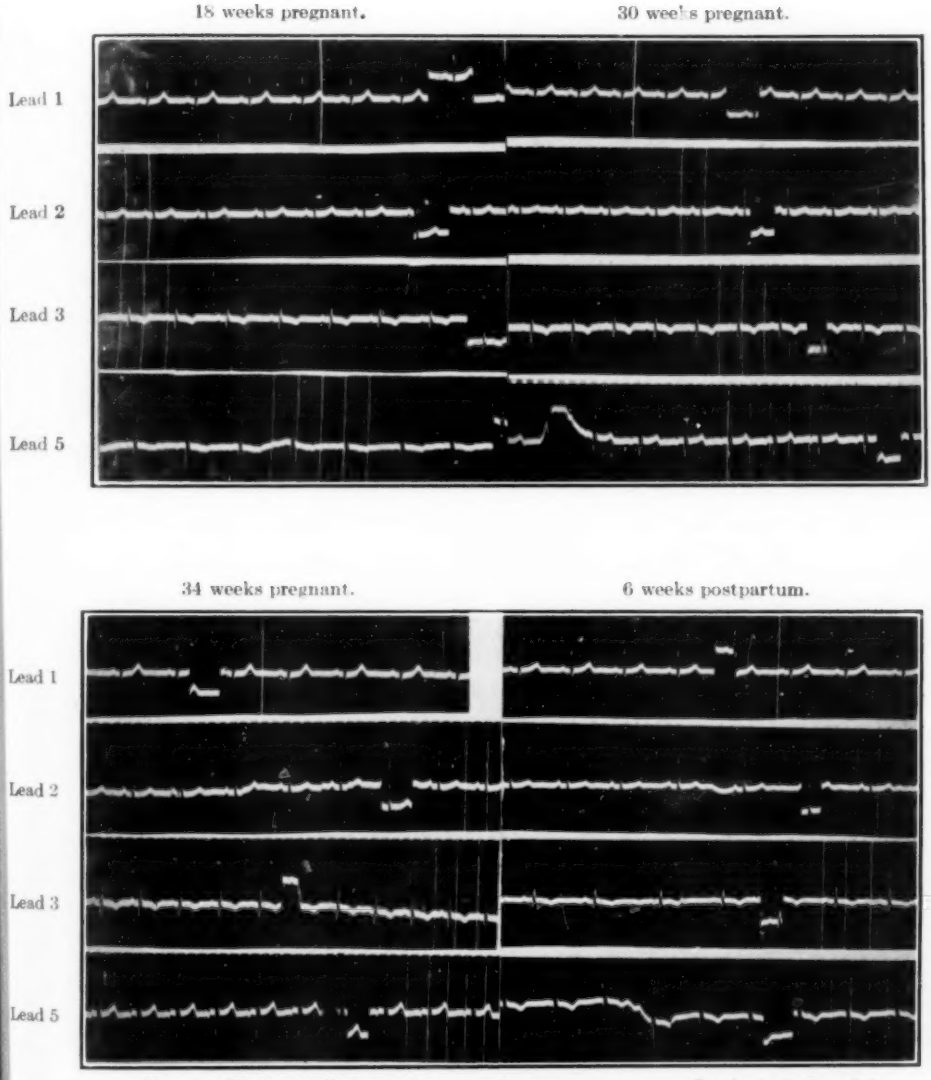
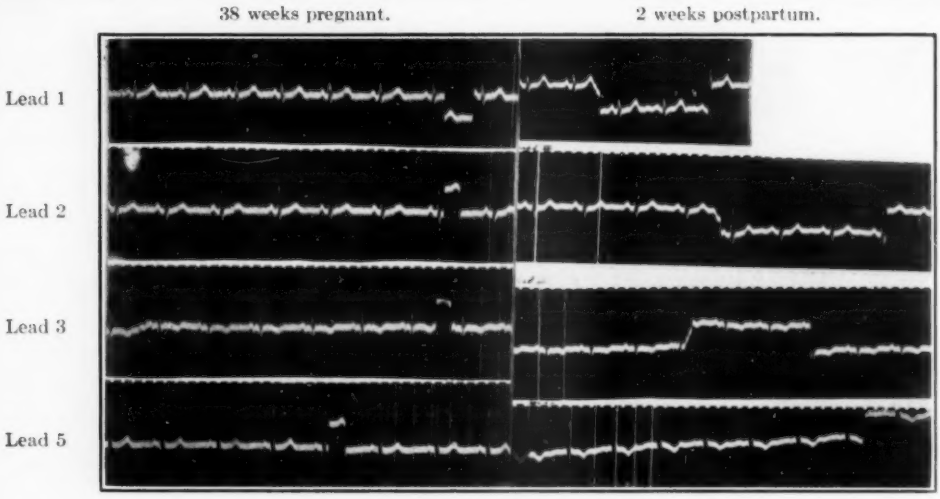
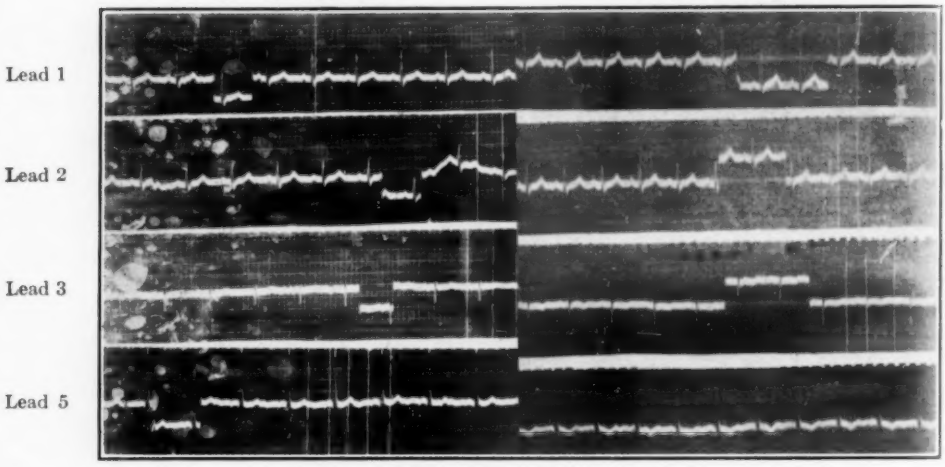


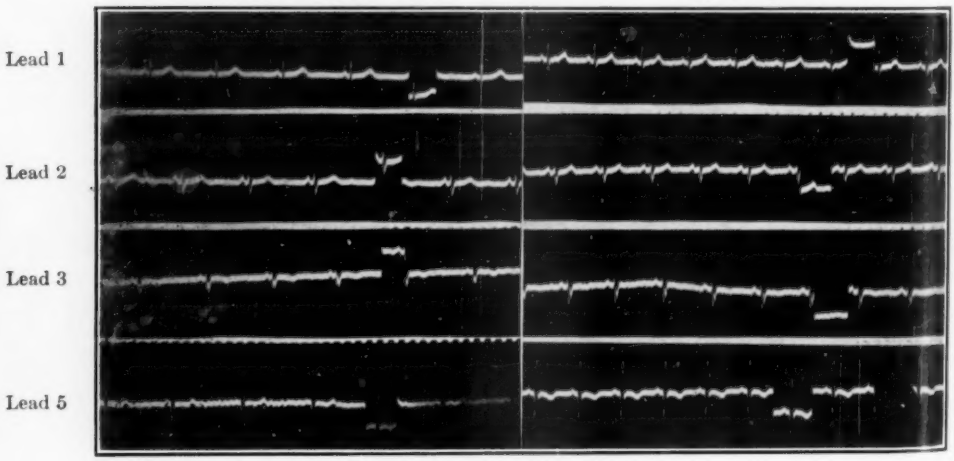
FIG. 1.—Electrocardiogram of a normal pregnant woman. Leads 1, 2, 3 and 5 of the electrocardiogram of a normal pregnant woman taken during pregnancy and puerperium. Upright *T*-5 and deep *Q*-3 developed during pregnancy, and returned to normal postpartum.



A. Rheumatic heart disease, mitral stenosis.



B. Coarctation of the aorta.



C. Toxemia of pregnancy.

All show upright *T*-5 during pregnancy with inversion postpartum.

FIG. 2.—Upright *T*-5 during pregnancy. Leads 1, 2, 3 and 5 of the electrocardiogram in 3 patients before and after delivery.

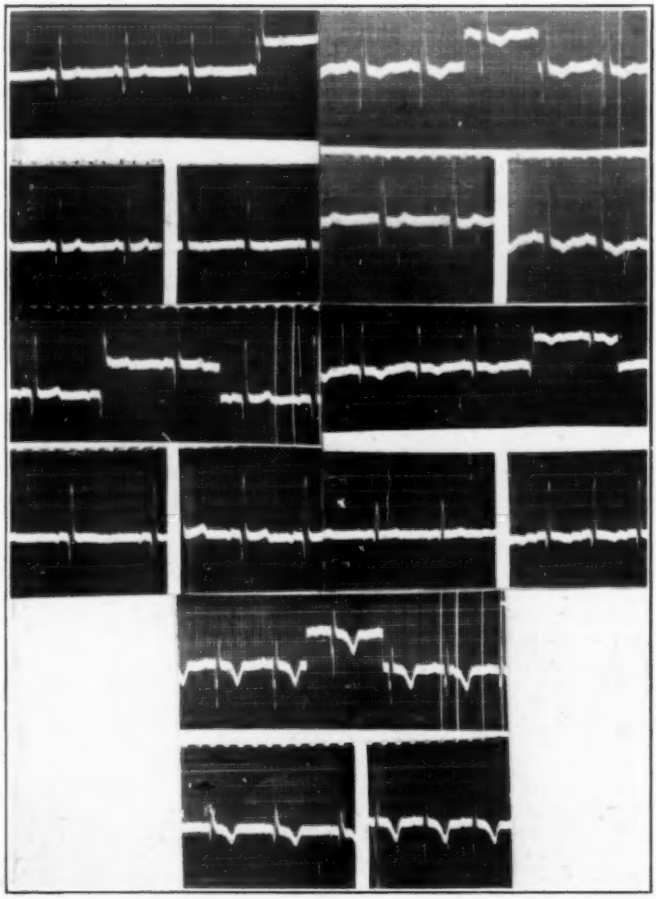


FIG. 3.—Effect of inspiration and expiration on Lead 5. Lead 5 of the electrocardiogram of 5 pregnant women. Of each set, the upper is taken in the usual manner, the left lower in deep inspiration and the right lower in deep expiration. There is no consistent change.

form, with patients who received digitalis excluded. The percentage is proportionately high in "toxemics," although the data are not sufficient for significant conclusions on this point. In all normal women on whom postpartum observations were made, the upright *T* wave invariably became inverted again. Absent *Q*–5 or *Q*–5 less than 2 mm. were observed both in cardiacs and in toxemics but in no normal cases.

Eleven deep *Q*–3's were observed, 5 being in normal pregnant women, making an incidence of approximately 5% of deep *Q*–3's in normal pregnant patients, which corresponds well with figures previously reported from this clinic.[3]

The *P* wave was quite variable. This was noted in 398 electrocardiograms of pregnant and puerperal women. In normal patients it was upright in 58 electrocardiograms, inverted in 60, diphasic in 13, flat in 15 and variable in 6. In cardiacs it was upright in 102 electrocardiograms, inverted in 66, diphasic in 24, flat in 11 and variable in 2. In the toxemia groups it was upright in 23 electrocardiograms, inverted in 11, diphasic in 3, flat in 4 and variable in 1.

One patient (Fig. 1) who was followed from the fourteenth week of pregnancy with monthly electrocardiograms and 7-foot heart plates was observed to develop an upright *T*–5 during pregnancy which disappeared after delivery. At practically corresponding times a deep *Q*–3 developed and disappeared. This correlation was not frequently noted, however. In 4 other patients deep *Q*–3 was associated with a diphasic *T*–5. Of these, 2 were normal women, 1 had hypertensive heart disease and 1 congenital heart disease. In normals, cardiacs of various types, and toxemics, cases were observed where *T*–5 became upright during pregnancy and inverted again after delivery. Figure 2 (*A*, *B*, *C*), showing electrocardiograms from a case of rheumatic heart disease, a case of coarctation of the aorta and a case of "toxemia," illustrates the point. Figure 1 illustrates the point in a normal case.

In the last year of the study, Lead 5 (in addition to the routine manner) was taken in deep inspiration and deep expiration. No constant findings were present (Fig. 3). It was observed that *T* waves which were inverted on quiet breathing became upright on inspiration. Changes in amplitude of *QRS* on expiration were observed as were changes, such as splintering, in configuration of *QRS* on inspiration. The most frequent finding was an increase in amplitude of *QRS* and an increase in negativity of *T* wave on expiration. *P*-wave changes were extremely varied.

In several patients, inspiration caused *Q*–5 to diminish appreciably and in 2 patients caused it to disappear completely. Of these latter, 1 patient was normal, the other had rheumatic heart disease, mitral stenosis.

In 1 case studied with simultaneous electrocardiograms and 7-foot plates where there was a definite change in the electrocardiogram

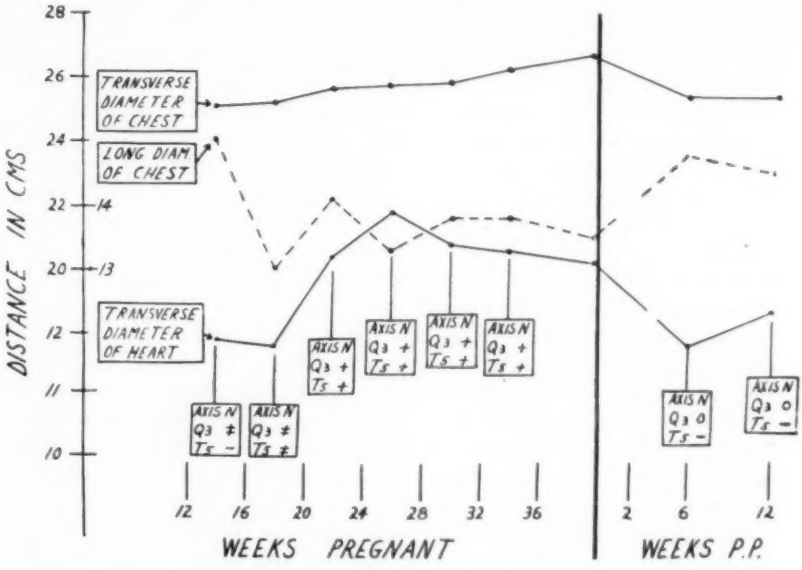


FIG. 4.—Electrocardiographic changes of a normal pregnant woman plotted in relation to *x*-ray chest diameters and transverse heart diameters. Electrocardiogram changes accompany changes in transverse heart diameter.

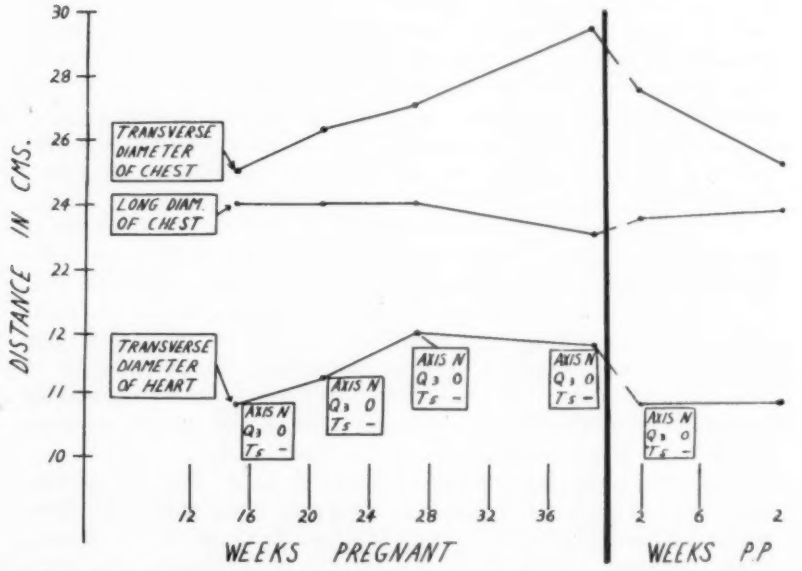


FIG. 5.—Electrocardiographic findings of a normal pregnant woman plotted in relation to *x*-ray chest diameter and transverse heart diameter. Neither electrocardiogram nor heart diameter changes significantly.

with a development of upright *T*–5's as pregnancy progressed, Roentgen ray showed concomitant changes in chest configuration; the diaphragm becoming higher and the lower chest becoming wider and the heart shadow larger (Fig. 4). In cases where similar observations were made and the electrocardiogram showed no change throughout pregnancy, it was noted that the chest showed no particular change and the heart shadow showed but slight change (Fig. 5).

Discussion. It can be seen then that in a certain percentage of cases, *T*–5 becomes upright as pregnancy progresses and inverts postpartum. Inversion of *T*–3 during pregnancy and return to normal postpartum has been described.[9] Sorsky and Wood[10] showed that an upright *T*–5 may be produced in approximately 50% of normal non-pregnant adults by moving the electrode towards or to the right of the sternum, that is, the position of the heart remains constant but the electrode is shifted. In pregnancy when upright *T* waves appear in Lead 5, it is probable that the same mechanism operates, the difference being that the electrode position is constant but the heart is shifted under it as pregnancy progresses. A shift in heart position during pregnancy has been suggested, as well as change in heart size;[1] changes in electrocardiogram are known to accompany change in heart position.[5]

The shift in heart position may not be the sole factor operating to change the electrocardiogram in pregnancy. The possible slight change in heart size must also be considered. In that respect it is of interest that the shift leftward in electrical axis during pregnancy, with return towards normal in the latter trimester,[2] parallels closely the change in heart volume described by Binhold[1] from orthodiograph studies, where there is increase in heart volume as pregnancy progresses with a similar return towards normal in the last trimester. Further, it is as yet unknown whether the profound circulatory, endocrine and nervous changes found in pregnancy influence the electrocardiogram. No evidence for or against the possibility that vitamin B deficiency was a factor in the *T*-wave changes appeared in these cases.

This study lends support to the accumulating evidence that certain changes in Lead 5 of the electrocardiogram, particularly upright *T* waves are in themselves not indicative of myocardial disease. Recognition of the changes which may accompany normal pregnancy and also inspiration and expiration may prevent erroneous electrocardiographic diagnoses of heart disease in normal pregnant women.

The addition of chest leads to the routine electrocardiographic study of pregnant women provided nothing of positive clinical importance. However, when the cause of the *T*-wave change in pregnancy is eventually determined, it may contribute more precise information to the study of changes in the heart and circulation in pregnancy.

Summary. 1. Lead 5 of the electrocardiogram was determined 398 times on 288 pregnant women.

2. The *T* wave was observed to be upright in 7.7 % of normal pregnant women.

3. Changes in the chest lead during pregnancy, particularly those in the *T* wave, were thought to be associated with changes in the position of the heart.

4. Lead 5 is of no particular value in diagnosis of heart disease during pregnancy.

5. Recognition of normal variation in Lead 5 of the electrocardiogram during pregnancy will avoid erroneous diagnoses of myocardial disease in pregnant women with normal hearts.

6. These conclusions apply only to chest leads taken with the electrodes placed in the manner described above, *i. e.*, exploring electrode in the fourth interspace 5 cm. to the left of the sternum, indifferent electrode on left leg, and do not apply necessarily to chest leads taken with the exploring electrode at the apex of the heart.

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NOTE ON A CASE OF CONGENITAL ABSENCE OF LEFT LUNG.

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Hurwitz and Stephens[1] tabulate 34 cases of this condition and add 1 more. In view of the facts that this abnormality is very infrequent, that one of us (A. G. E.) reported 21 years ago Case 20 in the table of the above authors, and that this is the first to be reported from this country, we now wish to report another case. This is from the Obstetric service of Dr. Term Bunnag in the Siriraj Hospital, Bangkok, who kindly permits publication. The tabulation and discussion of Hurwitz and Stephens cover the subject so thoroughly that not even a summary is offered here.

Case Report. Nang Liam's son, 1 day, male, born prematurely with breech presentation from a mother who was suffering from amebic dysen-

tery and polyhydramnios. The estimated development of the baby was about 32 weeks *in utero*. The weight was 1510 gm. The abdomen of the baby was enlarged and showed signs of fluid and it was diagnosed as congenital ascites. The baby cried once after delivery and became cyanotic and died.

FIG. 1.—Postmortem photograph showing single lung.

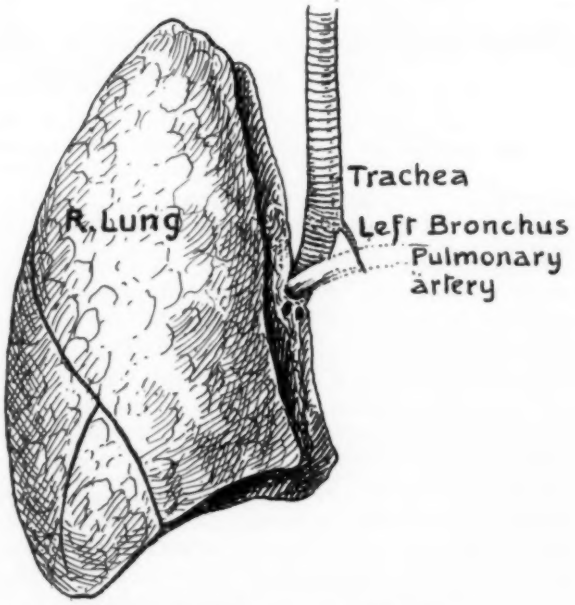

FIG. 2.—Drawing of arrangements at root of right lung.

Necropsy. The chest of this small baby is narrow and thin, the abdomen distended with fluid. There are about 100 cc. of clear yellowish fluid in the peritoneal cavity; the serous surfaces are smooth. The liver occupies

almost the whole upper part of the abdomen; the left lobe is larger than normal and there is also an azygos lobe on the posterior portion. There is no spleen; in the splenic area are a few spleen-like masses of tissue, purplish in color and a few millimeters in diameter. The intestine shows unusual rotation of the coils and the transverse colon is alongside the cecum and ascending portion.

The arrangement of the chest organs is abnormal. There is complete absence of left lung, the left pleural cavity being lined by thin parietal pleura and containing a small quantity of clear fluid. The heart is displaced to the left and occupies the space of the left pleural cavity (Fig. 1).

The right lung is connected with a normal right bronchus which is a continuation of the trachea. The lung tissue is soft and pale red and the size is larger than normal, the septa dividing the organ into four lobes.

The left bronchus is a rudimentary bud branching off from the trachea 2 mm. above the pulmonary artery and ending in a cul-de-sac; no lung tissue can be discovered (Fig. 2). This left bronchus is 8 mm. long; 1 mm. in diameter at the middle portion. The distal portion is small and tapers toward the end. The bud is soft and contains no cartilaginous rings.

The thymus is normal in shape and size. The pericardium is smooth and the cavity contains some fluid. The heart is normal in shape and size. The truncus arteriosus shows failure of division.

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A STUDY OF ORAL TYPHOID VACCINATION AS MEASURED BY BLOOD SERUM AGGLUTININS.

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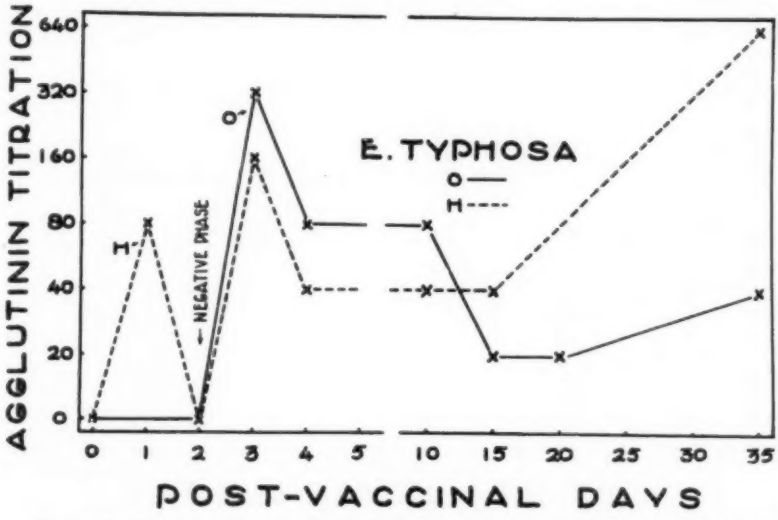
In this study, 200 patients were vaccinated with mixed typhoid vaccine. One-half of the number were vaccinated by the subcutaneous method and the other half by the oral method. Blood serum agglutinins were determined at various intervals.

Numerous studies of oral vaccination with the typhoid and dysentery organisms have been made on various laboratory animals. According to Calmette,[2] Pasteur's work with chicken cholera (1880) first suggested the possibilities of oral vaccination. Wright[4] was the first to attempt the oral method of immunization on human subjects. Besredka,[1] especially since the World War, has advocated his local immunity theory. This has given added impetus to the oral method of administering vaccine in the enteritides. The laboratory results have been varied and inconclusive. The first clinical application of the oral method of typhoid inoculation was in 1922.[1] Since that time over 500,000 cases of oral vaccination have been reported in the literature. The clinical results have been favorable and far more conclusive than the laboratory studies. Finder and

Simmons[5] present an excellent survey of the literature on oral vaccination. Recently, Lacy and Cohen[6] and Moor and Brown[7] have made similar studies of the two methods of administering typhoid vaccine, as measured by the agglutinin titration of the blood sera in human subjects. The latter used the same vaccine as reported in the present study.



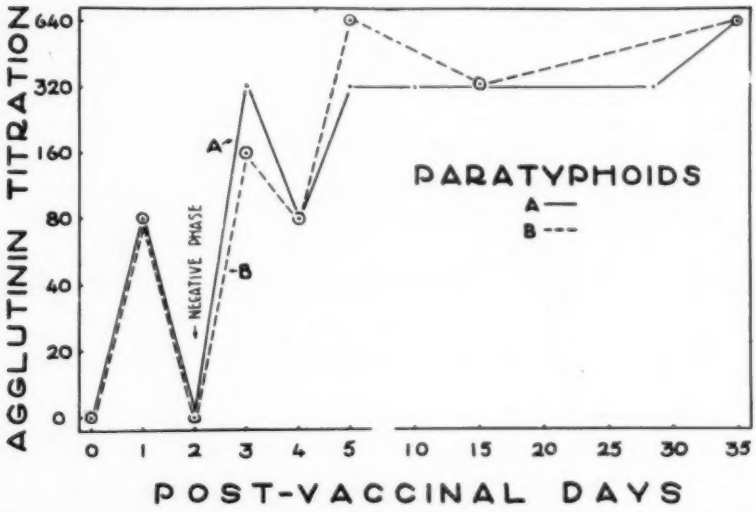
GRAPH 1.—Diagram showing the postvaccinal agglutinin changes in an individual following oral vaccine. This shows the manifestation, the induction phase and fluctuation of agglutinins of the "O" and "H" fractions of *E. typhosa*.

Methods. The oral and subcutaneous cases were unselected from a large group vaccinated during the Ohio River Valley Flood of 1937. The latter were given the mixed typhoid antigen subcutaneously in the usual series of 3 injections, each at an interval of 3 to 7 days. The agglutinins were then titrated 5 to 8 weeks following the completion of the vaccine injection.

Prior to administration of the oral vaccine, a history was obtained of previous vaccination, typhoid disease, or dysentery. A pre-vaccinal agglutinin titration was made. Following the oral vaccine, the agglutinins were again determined at 60 hours, 5 weeks and 6 months. Daily titers were determined on a number of the oral group, to determine the interval of agglutinin manifestation, the induction and the negative phase (which is prolonged by menstruation), together with the increase and fluctuation of the type specific agglutinins (Graphs 1 and 2).

The blood serum agglutinins were determined according to the method of Welch and Stuart.[10] This method was used because of its expediency and the comparable results with the macroscopic test tube method. Controls were made using normal saline with each series of the bacterial suspension, in order to avoid spontaneous agglutination. Agglutinin titers were made for both the somatic ("O") and the flagellar ("H") fractions of the *E. typhosa* (*B. typhosum*) antigens and the mixed antigen of *S. paratyphi* (*Paratyphoid α*) and *S. schottmülleri* (*Paratyphoid β*). Dilutions ranged from 1 to 20 to 1 to 2580. The higher dilutions are only gross approximations.

The oral antigen used in this study was Typhoral—mixed.* A capsule of bile salts (gr. $\frac{3}{4}$) was administered 1 hour and 45 minutes before breakfast. The first capsule of antigen† was given 45 minutes later. The second and third capsules were given on successive days (without bile salts) 1 hour before breakfast. Thus, the oral vaccination is completed in 3 days. If optimal results are to be obtained, particular care must be taken in following this procedure of administering the vaccine.



GRAPH 2.—Diagram showing the postvaccinal agglutinin changes for the paratyphoids in an individual following oral vaccine—mixed.

Results and Discussion. Of those cases (institution employee group) receiving oral vaccine, 19% had been vaccinated previously, 2% gave a history of typhoid and 11% were cases of arrested pulmonary tuberculosis. (The latter group shows a degree of nonspecific reaction to the typhoid agglutination tests). In view of this, a total of 32% of the cases would likely manifest some degree of pre-vaccinal agglutinins. Three cases, with a history of recent food poisoning, had high titers for *Paratyphosus* β. Eleven per cent of the subcutaneous cases gave a history of previous vaccination or typhoid disease. Following the administration of the oral vaccine, there were no severe reactions. Thirteen per cent of the cases had a slight febrile reaction, none of which was above 38° C.; 33% had some symptomatic reaction, but in no case was the individual incapacitated (Table 1).

Following an interval of 60 hours, the titers of the "O" antigen fraction are the lowest of the series, the majority of cases ranging

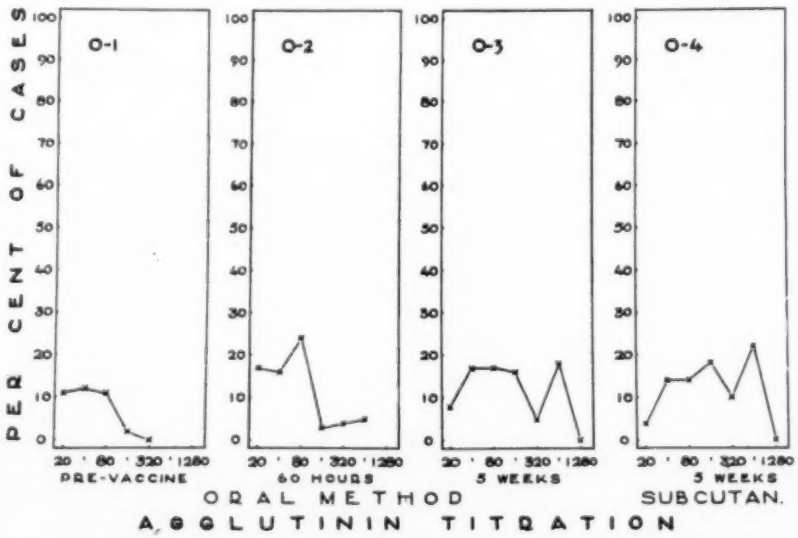
* Purchased from Eli Lilly Co., Indianapolis, Ind.

† Ten thousand million typhoid bacilli; 5000 million *Paratyphoid* α bacilli; 5000 million *Paratyphoid* β bacilli.

from 1 to 20 to 1 to 80. After an interval of 5 weeks the "O" titers continue to be the lowest of the series, but have increased both in number of cases and titration (Graph 3, 0–3). The histograms of the oral and subcutaneous cases, at 5 weeks, are essentially comparable (Graph 3, 0–3 and 0–4).

TABLE 1.—SYMPTOMS FOLLOWING ORAL TYPHOID VACCINE—100 CASES.

Symptoms.	Cases.
Headache	14
Nausea	6
Malaise	4
Emesis—first capsule	3
Diarrhea—slight	2
Tenesmus	1
Orbital edema	1
Joint pains	1
Vertigo	1
Total	33

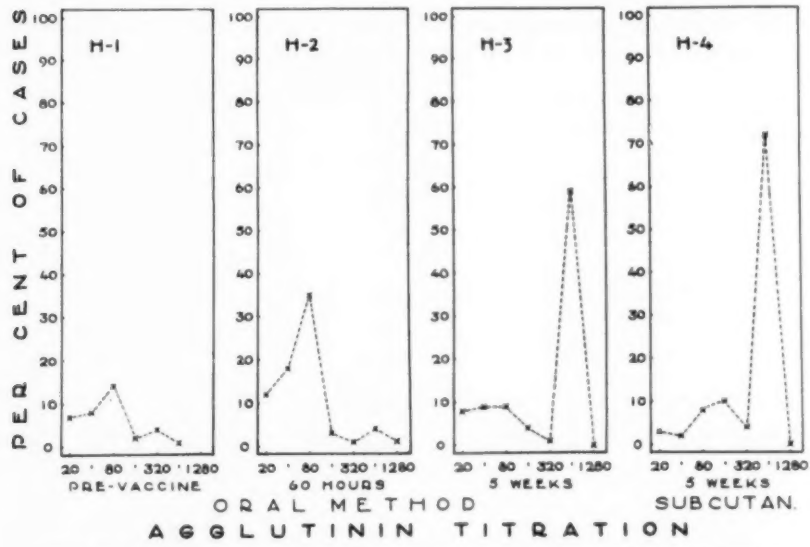


GRAPH 3.—Diagram showing distribution of cases according to agglutinin titration with the somatic antigen "O" of *E. typhosa* following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).

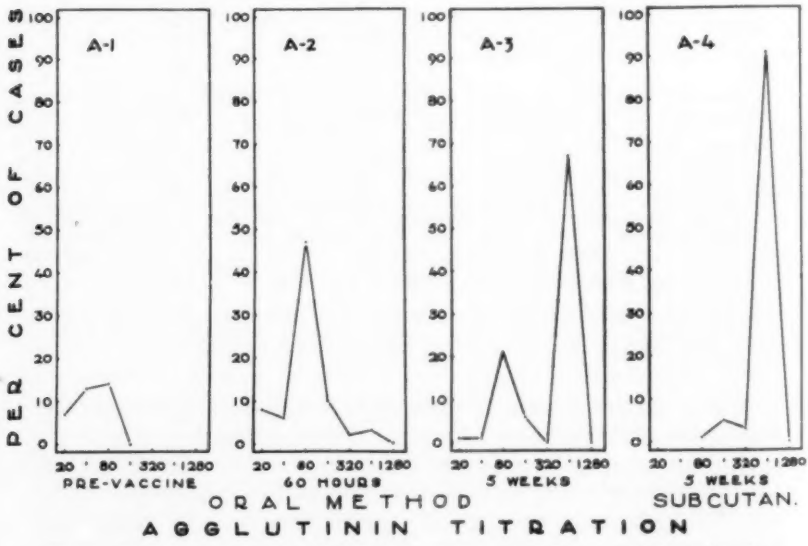
The maximum number of cases showed agglutinins with the "H" suspension in dilutions of 1 to 80 at 60 hours (Graph 4, H-2). The agglutinin titration increased to 1 to 640 at 5 weeks (Graph 4, H-3). This is contrary to the findings of Dennis and Berberian[3] who found the "O" agglutinins were usually higher than the "H" agglutinins following oral vaccination.

In both the oral and subcutaneous methods, the "O" and "H" fractions of *E. typhosa* tend to be slower in the appearance of their agglutinins than do the paratyphoids.

The greatest number of cases responded to *Paratyphoid* α at 60 hours in dilutions of 1 to 80 (Graph 5, A-2) and to *Paratyphoid* β in

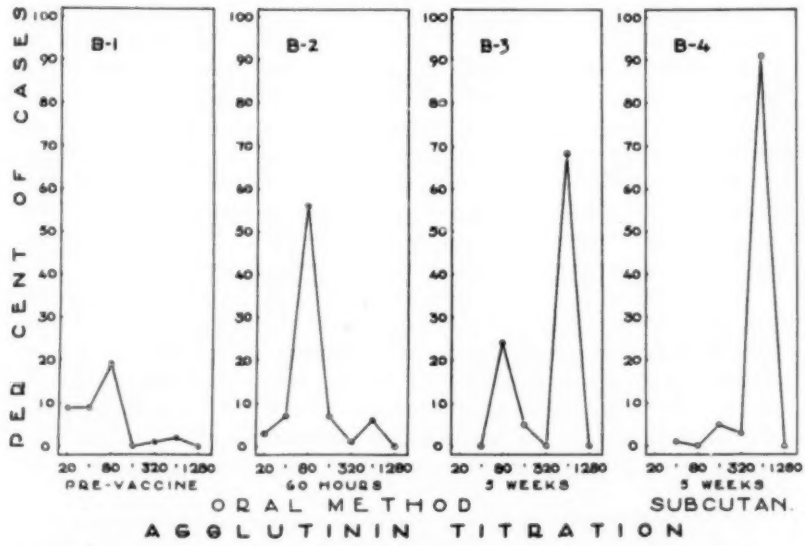


GRAPH 4.—Diagram showing distribution of cases according to agglutinin titration with the flagellar ("H") antigen of *E. typhosa* following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).

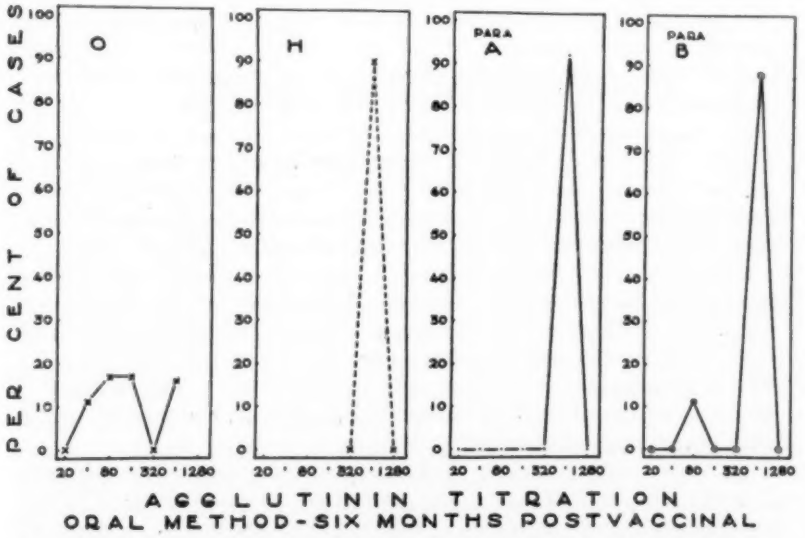


GRAPH 5.—Diagram showing distribution of cases according to agglutinin titration with the antigen of *S. paratyphi* (*Paratyphosus* α) following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).

dilutions of 1 to 80, but in greater numbers than with *Para* α (Graph 6, B-2). This demonstrates the well established fact that *Para-*



GRAPH 6.—Diagram showing distribution of cases according to agglutinin titration with the antigen of *S. schottmülleri* (*Paratyphosus* β) following administration of typhoid vaccine—mixed (oral method, 100 cases; subcutaneous method, 100 cases).



GRAPH 7.—Diagram showing the persistence of typhoid agglutinins in the blood serum 6 months following oral vaccine.

typhoid α is less agglutinable than is *Paratyphoid* β. This is more apparent in the qualitative evaluation of the agglutinins. At 5 weeks both of the paratyphoids have the greatest number of cases with agglutinins in dilutions of 1 to 640, which is somewhat higher than is generally reported for the paratyphoids following vaccination. With the paratyphoids, about 20% more subcutaneous than oral cases developed agglutinins in the higher dilutions.

The agglutinin response following the oral method is shown almost simultaneously with the administration of the antigen. Generally speaking, significant titers are present at 60 hours following oral vaccine. The titers are higher following a single subcutaneous dose than following a single oral dose of vaccine. *The titers following the two methods are essentially comparable after 5 weeks.*

In the reëxamination of the oral cases, following a post-vaccinal period of 6 months, significant titers were present in the "O" fraction in 61% of the cases, in the "H" fraction in 90% and in each of the paratyphoids in 92 and 99%. There was a moderate recession of the "O" agglutinins, a progression of the "H" fraction, while the *Paratyphoid* α had increased in both numbers and titrations. *Paratyphoid* β showed slight gain in both cases and agglutinin titer (Graph 7).

In the present study, after a post-vaccinal period of 5 weeks, 24% of the subcutaneous and 8% of the oral cases failed to show agglutinins. This is in striking contrast to the recent report of Lacy and Cohen[6] who reported the absence of agglutinins in 25% of the subcutaneous and 93.4% of the oral cases. The variance of results can best be accounted for by the difference in the antigen strains employed in the preparation of the respective vaccines. Lacy and Cohen[6] used their own laboratory strain of organisms, which was formalinized in the preparation of their oral antigen.

In the preparation of a mixed typhoid vaccine, according to Topley,[9] the organisms should possess the following characteristics: *B. typhosum*—smooth, motile, virulent strain, with flagellar antigen and surface antigen III; *B. paratyphoid*—smooth, motile, virulent strain, with flagellar antigen and surface antigen VI.

The Typhoral—mixed (Lilly) vaccine, according to the manufacturer, is prepared from the new U. S. Army Strain No. 58, as reported by Siler[8] and "a virulent local strain, which caused a fatal case." Both are considered superior to the old Rawling strain. The organisms are heat killed and preserved with "Merthiolate." Moor and Brown[7] used the same oral antigen as the present study with equally favorable results.

In view of the favorable clinical reports, the agglutinin response and the reduction of constitutional symptoms (as evidenced in the present study), the authors conclude that the oral method of typhoid vaccination merits favorable consideration and wider use.

Summary. 1. Using typhoid-mixed vaccine, 100 cases were vaccinated by the oral and a like number by the subcutaneous method. Blood serum agglutinins were determined periodically.

2. Thirty-three per cent of the cases which received the oral typhoid-mixed vaccine had mild reactions, none of which were incapacitating.

3. Significant agglutinin titers with oral typhoid vaccine are present within 60 hours. The agglutinin titration of both methods are essentially comparable after an interval of from 2 to 5 weeks. Significant titers persist for 6 months or longer following oral vaccine.

4. Those cases failing to show agglutinins 5 weeks following vaccination were 24% for the subcutaneous and 8% for the oral cases. Thus, the failures are three times as numerous with the subcutaneous as with the oral method.

5. The authors conclude, from the extensive clinical reports of others and the present laboratory results, that the oral method is as efficacious as the subcutaneous method of mixed typhoid vaccination.

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ACUTE INFECTIOUS GASTRO-ENTERITIS.

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With the apparent increase of acute digestive upsets associated with diarrhea, it would seem advisable to consider some of the problems presented by these cases. Certainly, we must agree that few conditions encountered by the physician in his daily rounds are as puzzling from the standpoint of an etiologic diagnosis as those associated with the acute onset of diarrhea. Diarrhea is only a symptom of disturbed intestinal function and may be produced by many conditions both within and without the bowel.

If our clinician be a careful systematic worker, he will, when confronted with a case of diarrhea, patiently go over the history, developing a clear story of the onset and progress of the symptoms, searching for any etiologic factors in dietary irregularities, group exposures, and so on. He will then make a complete physical exam-

ination, inspect the stools, and check the blood count. While doing these things, he will run over in his mind the various possibilities excluding many and restricting his preliminary diagnosis to a relatively small number. This number may be further decreased by stool cultures, agglutination tests, phage tests, and so on, but all too often after having done his utmost he will be forced to a diagnosis of diarrhea of unknown etiology.

If, on the other hand, our clinician is hurried or a bit casual or by past experience convinced that an etiologic diagnosis is unlikely, he will attempt to exclude the acute surgical conditions and then will readily accept the patient's statement that his symptoms are due to some food that he has eaten, or that he is suffering from intestinal "flu." However, the physician must frequently admit to himself the diagnosis of diarrhea of unknown etiology. Fortunately, these cases are usually relatively mild and of short duration so that insofar as the patient is concerned, he rarely suffers any ill effects from his incomplete diagnosis. On the other hand, from the physician's standpoint it is certainly a challenge to modern medicine that a condition approaching epidemic proportions is so frequently unexplained.

We have recently experienced in the San Francisco Bay area a fairly widespread outbreak of acute gastro-enteritis, both in institutional groups and the general population. These cases have been characterized by the acute and sudden onset of nausea, abdominal cramps, watery diarrhea, sometimes vomiting, slight headache, general aching, dizziness, and fever. In some cases there have been mild upper respiratory symptoms for a day or two before the explosive onset of the digestive symptoms. The most characteristic symptom was the explosive watery diarrhea, the number of stools varying from 2 to 20 or more per day. Tenesmus was rare and blood or mucus was very rarely seen in the stools. Temperature varied from normal to 104°. The average case was relatively mild and of short duration. However, complications may occur as evidenced by the development in 2 of our cases of acute appendicitis requiring operation.

During the last year, we have seen sporadic cases of this condition with greater frequency than in previous years but during the first part of December it approached epidemic proportions. Thus, at the Stanford University Hospital, 28 nurses and several members of the general hospital personnel were hospitalized for this type of disturbance between November 16th and January 15th, 20 of the admissions occurring between the 9th and 16th of December. During the same period a considerable but undetermined number of the hospital personnel were similarly affected but did not report for hospitalization. While this was occurring at Stanford Hospital, other institutional and industrial groups as well as the general population about the Bay area were experiencing the same difficulties.

The period of hospital confinement in this group of 28 nurses varied from 2 to 13 days with an average of 4.8 days. This does not include the hospital days for complications, nor have we figures for working days lost in this group after dismissal from the hospital nor for the days lost by those not hospitalized. However, these figures sufficiently emphasize the economic drain connected with such an outbreak.

Turning to a more detailed analysis of the symptoms in our cases, we find diarrhea present in all. The stools varied from 2 to 17 per day, were usually small, watery, light yellow, free from mucus and gross inflammatory elements, although showing an increase in pus cells microscopically. One of our cases showed macroscopic blood in the stools and I am informed that several cases reporting at the emergency hospital also showed blood in the stools.

Fever was present in 25, ranging from slight to 104°, usually dropping sharply to normal in 2 or 3 days. Abdominal cramps usually preceded the bowel movements and at times were quite severe. The bedside records mention the occurrence of nausea, vomiting, headache, backache, nasal congestion, sore throat, and chills.

Careful blood counts were made by Dr. Wyckoff's staff at Stanford University Hospital on 25 of these patients; 14 showed white blood counts under 10,000, 8 ran from 11,600 to 14,500, and 3 ran over 20,000. The polymorphonuclears varied from 37 to 93%, 9 being below 65% and 16 above 65%; 22 had a definite left nuclear shift with a banded count of 10% or higher; 62% was the highest relative count and 10,971 was the highest actual banded count. Eight cases had an eosinophilic count ranging from 1 to 7%, the highest actual eosinophilic count being 1248. Dr. Wyckoff calls attention to the fact that it is unusual with a left nuclear shift to have the eosinophilic elements persist and that this is not ordinarily seen with bacillary infections. From these counts, it is evident that our cases present no characteristic blood picture.

Stool cultures were carried out on 13 cases. In 10, there appeared a growth of Gram-negative bacilli giving the sugar reactions of the typhoid-dysentery group but as yet defying exact classification. In the serologic tests using *B. typhosus*, *B. Flexner W*, *B. Flexner Z*, *B. dysenteriæ Y*, and *B. dysenteriæ Sonne*, antisera, there was but one agglutination that might be taken as significant.

We were frankly surprised to find the high percentage of cultures showing the characteristics of the typhoid dysentery group but still did not feel convinced of their etiologic importance. Further cultural studies are being carried on, but when it is recalled that there are probably about 50 types of dysentery bacilli divided among 3 main groups 1, Shiga; 2, Flexner, and 3, Sonne—having different cultural characteristics, the difficulties of pursuing this study in a busy laboratory are evident. An additional difficulty

in evaluating the etiologic significance of these organisms is that some of these atypical strains will not agglutinate with the standard type sera, so that the diagnostic value of the agglutination test is greatly decreased. Negative agglutination tests may be obtained in proven cases of bacillary dysentery if the laboratory does not include in its test antigen a strain similar to the one causing the infection.

Probably the most valuable use of the agglutination test in determining the etiologic significance of a specific organism isolated from the stool is to attempt to agglutinate it against the patient's own serum after his recovery. This test was carried out on 10 of these cases with negative results in all. Such a result certainly makes it seem unlikely that these organisms were the cause of the infection and much more likely that they were merely accidental invaders.

From this brief review of these cases which were in all ways apparently similar to cases occurring in other institutions and the general population about the Bay area, it seems evident that we were dealing with an acute infectious gastro-enteritis of undetermined etiology.

Outbreaks of diarrhea are all too common in isolated institutions and can frequently be traced to food poisonings or to infection with one of the bacillary dysentery group. In connection with such outbreaks an important possible source of infection has recently been called to our attention by the sanitary engineers. Largely stimulated by the outbreak of amebiasis in the Chicago hotels, the whole subject of contamination of the water supply within buildings has been carefully studied and many surprising possibilities brought to light. Thus, any plumbing fixture in which the intake pipe takes off directly from the supply pipe and enters below the highest water level in the container may under certain conditions act as a syphon and draw the material in the container directly into the supply pipes. All that is necessary is that there shall be a temporary vacuum in the supply pipe such as is produced by shutting off the pressure in the mains, draining the supply pipe in a dwelling, or, in large buildings, by sudden excessive use on the lower floors. As a public health menace, the flush valve type of toilet is the most dangerous and it has been demonstrated that frequently this syphonage does occur.*

I recently spent some time with Dean Morris of the Engineering Department of the Stanford University and he had some interesting stories to tell. In one of the most modern homes on the campus equipped with the latest bathroom fixtures, it was demonstrated that coloring matter placed in the toilet bowl on the second floor

* Plumbing regulations now in force in most communities require the presence of a syphon breaker in all new flushometer valve installations. The danger of syphonage, of course, continues in older fixtures not equipped with the syphon breaker.—EDITOR.

could be recovered from the water faucet in the kitchen by merely shutting off the street supply valve and drawing water on the lower floors. A somewhat similar but more dramatic demonstration was the plumber who was called to repair a toilet that refused to drain; having inspected it, he went to the basement, shut off the supply valve, and drained the pipes. Imagine his surprise but hardly gratification when, on returning to the disordered toilet, he found it emptied, the contents having been syphoned back into the water pipes. There are many more stories, illustrating the possibility of contaminating the water supply if a negative pressure occurs in the supply pipes. At Claremont Colleges, they are convinced that since the correction of their plumbing arrangements, they have been free from the recurring outbreaks of diarrhea present before.

In this connection, the following letter from Dr. J. R. Griggs, the college physician at Claremont Colleges, is of interest. He states that "prior to the change in our plumbing system we have had epidemics of gastro-enteritis in which several dozen students would be simultaneously disabled with vomiting, diarrhea, abdominal cramps, fever 100–103, headache and varying degrees of toxicity. Most of them were ill for twenty-four hours to several days and were quite weak on recovery. Such outbreaks occurred usually in October or November and were repeated once or twice during the year. Apparently they became progressively worse gradually over a period of many years. Between the epidemics there were practically always individual sporadic cases of the same disease.

"Repeated samples of water and milk for culture failed to reveal the cause of the trouble. A great variety of causes and sources were suspected. A few cases occurring among townspeople led to the belief that the whole city water supply was contaminated by alvine discharges from the mountain cottages up the canyon. The method of fertilization and spray of the fresh vegetables and fruits was incriminated. Food handlers were scrutinized. Even the Santa Ana winds from the desert were suspected as the cause. The County Health Department repeatedly investigated and gave the colleges a clean bill of health.

"After much collaboration with pathologists, epidemiologists, and sanitary engineers it was found that eosin placed in toilet bowls could be recovered in the tap water because of back siphonage. Accordingly, vacuum breakers were installed on all toilets of the flushometer type in all college buildings, last year.

"Since September when I came here, we have had no epidemics of the old disease. In fact, no more than 3 persons have been ill at any one time with gastro-enteritis of any nature. Only 2 cases have approached the severity of the old 'plague.' There have, however, been nearly two dozen single sporadic cases of diarrhea, some with nausea, scattered throughout the past semester and throughout the student body of 1000 students. Two cases occurring

together were traced to an outside eating house, Mexican. Several others came back from holidays into Mexico. Two others were traced to homecured raisins. The rest have apparently originated here but have not had any epidemic characteristics."

Confirming these reports, W. Scott Johnson recently made a survey of 6 milk plants in St. Louis and found "210 definite plumbing defects which were capable under favorable conditions of establishing cross connections between contaminated material and the plant water supply." He further states that "it is recognized that a partial vacuum may exist without warning in any water pipe system due to a number of causes such as a heavy drain in a main due to a fire or cutting off the water supply and draining lines for repairs. Such a vacuum has been shown to be capable of siphoning the contents of a flush valve type of toilet bowl in good working order into the water supply line." It is thus evident that there is a very definite public health problem connected with our modern plumbing and that constant vigilance is necessary.

In this particular outbreak, it seemed too widespread to be satisfactorily explained on the basis of a bacillary dysentery or a food poisoning. Turning to the literature for a possible explanation, we find that R. R. Spencer[1] under the title of "Unusually Mild Recurring Epidemic Simulating Food Infection" reported apparently similar cases. In 1933, H. A. Wildman[2] under the title of "Polytropous Enteronitis" (acute infectious gastro-enteritis, or Spencer's Disease), reported a study of 750 apparently similar cases occurring in college students between September, 1927, and June, 1932. From his study he concludes that this condition may occur at any time of the year, either in epidemic or sporadic form, that it is widely distributed, uninfluenced by climate, that no predisposing factors have been determined and the responsible organism is unknown, and that it is apparently spread by secretions from the nose and throat.

Atypical colon bacilli, atypical Flexner bacilli, and atypical organisms belonging to the genus Salmonella have been found in the stools though their presence may be purely coincidental.

He calls attention to the fact that epidemics of diarrhea have been frequent since the World War, and have occurred in close association with epidemics of influenza. Influenza does not confer immunity to this disease or *vice versa*. Immunity after this disease did not last more than 6 weeks in some cases. Cases developed within 24 to 48 hours after contact with a known case, and epidemics reached their peaks in from 3 to 5 days instead of from ½ to 12 hours as occurs in food poisoning.

About 10% of his patients complained of respiratory tract symptoms. He noted the frequency of peripheral neuritis. Blood counts showed polymorphonuclear leukocytosis, sometimes followed by a secondary leukopenia. Acute symptoms usually lasted from 18 to

24 hours and were followed by rapid recovery although the diarrhea has lasted 2 or 3 weeks and marked dizziness in standing has lasted as long as 6 weeks in some cases.

He has divided his cases into six groups in the order of their frequency: Type I: Gastro-enteric: nausea, vomiting, diarrhea. Type II: Enterocolic: diarrhea, sometimes cramps. Type III: Gastric: anorexia, nausea, vomiting. Type IV: Neurocirculatory: dizziness, dull headache. Type V: Typhlo-appendiceal: like acute appendicitis except for diarrhea; dizziness on standing, dull headache, fever less constant, less marked and less sharply localized tenderness in lower right quadrant, and less rigidity of abdominal wall. Type VI: Colic: cramps or severe midabdominal pain, usually with constipation.

At Wooster College, Imlay, Michigan, the author reports from 3 to 5 distinct epidemics each year with a large number of sporadic cases through the year. There were no fatalities and no sequelæ. Occasionally, a case of acute appendicitis occurred as a complication.

Treatment at present is naturally purely symptomatic. Wildman, from his experience recommends: 1. Prompt and thorough evacuation of the intestinal tract with castor oil, 1 ounce; soda bicarbonate 1 ounce; and orange juice. 2. Abstinence from food for 24 hours. 3. Cleansing enema, 2 ounces of salt to a quart of water. 4. Atropine, 1/100 grain to 1/50 grain for nausea or vomiting. 5. Soft, bland diet later. 6. Sodium ricinoleate, from 18 to 120 grains in divided doses, after the castor oil. 7. Bismuth subnitrate. 8. Camphorated tincture of opium. 9. For dizziness: (*a*) abdominal binder; (*b*) ephedrine, $\frac{3}{8}$ grain. 10. Phenobarbital, and so forth, for nervousness. 11. Aspirin. 12. Salt solution subcutaneously. 13. Glucose solution intravenously.

From this review, it is evident that there is a fairly widespread gastro-enteritis occurring sporadically and at times in epidemics, of uncertain etiology, running a fairly typical course of short duration, and usually terminating in complete recovery. None of the atypical organisms so far reported in the stools can be accepted as of proven etiologic significance although there is room for further study. There is much to suggest that the primary infection in these cases is due to a filterable virus transmitted in the secretions from the nose and throat. The various organisms cultured from the stools are possibly only secondary invaders, such as the influenza bacillus has proven to be in influenza, and the various bacteria found in the nose and throat are in the common colds.

If we are dealing with a specific infectious gastro-enteritis due to a filterable virus, it is to be hoped that this will not show an increasing epidemic occurrence and the development of serious complications such as accompanied the pandemic of influenza.

My object in presenting this report is merely to emphasize the uncertainties that exist and to urge further discussion and research.

It is not a problem to be solved by the individual clinician, but his help is necessary in making promptly available to the public health and research laboratories material for study. From such a study it is reasonable to hope that information will eventually be forthcoming which will aid us as clinicians in more intelligent prevention, diagnosis, and treatment of acute gastro-enteritis.

Summary. 1. Acute gastro-enteritis seems to be occurring more frequently, both sporadically and in epidemics.

2. Many of these cases are diagnosed as diarrhea of unknown etiology.

3. Our modern plumbing offers many opportunities for contamination of the water supply within industrial plants, office buildings, and private dwellings.

4. It is suggested that there is an acute infectious gastro-enteritis probably due to a filterable virus, carried by the secretion of the upper respiratory tract.

5. It is urged that all outbreaks of diarrhea be reported immediately to the proper authorities for careful investigation.

6. With the accumulation and spread of more exact knowledge many outbreaks may be prevented.

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THE ETIOLOGY OF EFFORT SYNDROME.*

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Effort syndrome is a symptom-complex characterized by breathlessness, sighing, "dizziness" or "faintness," fatigue, palpitation, tachycardia, precordial pain and tremor, and is precipitated by exertion or anxiety. It is probably the commonest source of error in the differential diagnosis of organic cardiac disease. While it has been well recognized that effort syndrome is frequently associated with anxiety states, its etiology has remained obscure. Sir Thomas Lewis[43] suggested that a diminution in the buffer substances in the blood was a possible cause. More recently, especial attention has been given to the symptoms of sighing and of the related respiratory disturbances. White and Hahn[71] found that

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80% of 100 patients suffering from effort syndrome sighed excessively, whereas only 19% of 400 normal controls showed the same phenomenon. These writers stated that the total ventilation in at least one of their patients was normal, although from recent work on respiration by Shock and Soley[66] it becomes evident that she was hyperventilating. Baker[4] studied a group of patients with the symptoms of sighing, breathlessness, fatigue, palpitation and inframammary pain and concluded that the etiology was obscure and "treatment by no means always successful." Maytum and Willius[48] were the first to recognize the relation of hyperventilation to the symptoms described by these and many other authors.

Under the leadership of Dr. W. J. Kerr, a series of studies on the anxiety states and the hyperventilation syndrome has been carried out at the University of California Hospital.

Our purpose in this paper is to point out the relation of the symptoms of patients suffering from effort syndrome to the respiratory disturbances and to the shift in the acid-base equilibrium resulting from excessive loss of carbon dioxide from the lungs. Some or all of the symptoms of which these patients complained were reproduced by deep breathing at the rate of 25 to 30 respirations per minute. However, even when this respiratory rate was maintained, the symptoms were relieved when 2% CO_2 was added to room air, and the sensation of suffocation disappeared and breathing became subjectively easier.

In view of these findings, it was felt that a study of the acid-base equilibrium of the blood of these patients might show (1) whether a relative respiratory alkalosis was present chronically, and (2) whether the symptoms were related to the acid-base balance. Hence, acid-base determinations of the blood of 7 patients were made under basal conditions and during a period of voluntary hyperventilation in which their symptoms were precipitated. We are reporting in detail the history and experimental results in 1 of these patients, and are including charts (Fig. 3) demonstrating the changes in the pH, pCO_2 (CO_2 tension) and blood bicarbonate in 6 other cases.

Case History. E. C. B., a 27-year-old white, divorced housewife, first came to the University of California Clinic on June 2, 1932, complaining of palpitation. For several years she had been afflicted with palpitation, shortness of breath, dyspnea on exertion, precordial pain and fatigue.

There were no familial diseases. Both parents were living and were supported by the patient.

She had had the usual childhood diseases. Tonsillectomy and adenoidectomy had been performed at the age of 10, and appendectomy at the age of 22. In 1931, she had had a spinal injury. She had been married in 1925 and divorced shortly afterwards. She had 1 child living and well. There had been no other pregnancies.

On examination, the patient was found to be a well-developed and well-nourished woman. Many teeth were carious. The thyroid was thought to be slightly enlarged. A soft systolic murmur was heard at the apex.

The blood pressure was 120 mm. Hg. systolic and 86 diastolic. The examiner stated that there was possible left-sided cardiac enlargement and questionable edema of the ankles.

Laboratory. The first specimen of urine was acid, contained no albumin, showed green reduction, and contained 8 to 10 white blood cells in the sediment per high-power field; a later specimen was acid, had a specific gravity of 1.030, and contained no albumin or sugar and only an occasional white blood cell per high-power field. The Wassermann reaction of the blood was negative. Fluoroscopy showed the heart to be normal in size. An electrocardiogram showed a rate of 100, *P–R* interval of 0.19 second and inverted T_3.

Course. The patient was admitted to the hospital in August, 1932, for further study. Laboratory procedures on entry gave the following findings: Blood: 78% hemoglobin, 4,750,000 red blood cells, 7,680 white blood cells; the smear and differential count were normal. The stool was normal. Basal metabolic rate was 3%+. Dental roentgenograms showed several fractured root fragments, pyorrhea and one apical abscess. Diagnoses were made of (1) neurocirculatory asthenia and (2) dental caries.

After her discharge from the hospital the patient was followed in the clinic. In November, 1932, she strained her back. Later she received treatment for a retroverted uterus and menorrhagia. In March, 1935, there was a normal P.S.P. excretion by the kidneys. In May, 1935, a Webster suspension of the uterus was done because of low abdominal pain.

In December, 1936, she was able to give a much more accurate story of the symptoms which had bothered her persistently since she was first seen by us. She stated that these symptoms came in attacks which began with difficult, deep breathing followed by rapid heart rate, dizziness, constriction of her throat, suffocation, numbness of her hands and feet, extreme fatigue and finally diuresis. All of these symptoms were reproduced by a short period of hyperventilation (about 2½ minutes) and were relieved when she continued to hyperventilate while breathing CO_2. At this time physical examination was essentially negative. The thyroid was palpable but was normal in size. Fluoroscopy showed a heart of normal size with slight prominence of the pulmonary conus. On December 21, 1936, her basal metabolic rate was 9%+. A gastric analysis was normal. An electrocardiogram was normal. Fear of discovery of her illicit relations with several male acquaintances, as well as exertion, definitely initiated her attacks.

The final diagnosis was "anxiety state complicated by the hyperventilation syndrome." She was treated by explanation and demonstration of the cause of her symptoms, by administration of bromides and ammonium chloride, and by instruction in abdominal breathing and in the use of a paper bag for rebreathing during attacks. She improved rapidly and had only mild attacks occurring rarely until she was last seen on August 17, 1937.

Experimental Method. The subject, E. C. B., was brought to the laboratory in a fasting condition. After a rest of 45 minutes, the basal metabolism was determined in triplicate by the Tissot open-circuit method using a Siebe-Gorman half-mask. Six determinations each of pulse rate and blood pressure were made during this period. After the last metabolism sample of 10 minutes, the mask was removed and a control blood sample drawn from the finger tip for estimation of the acid-base balance of the blood by the Shock and Hastings micro-methods.[65] After the patient had rested 5 minutes, the mask was readjusted and voluntary overbreathing at the rate of 28 to 32 respirations per minute was begun and maintained for 10 minutes. The expired air was collected continuously in 2-minute samples for measurement of the respiratory volume and analysis of CO_2 and O_2 content by the Haldane technique. One-half-cc. samples of blood

were drawn from the finger tips at 2-minute intervals during the period of hyperventilation. After the cessation of overbreathing, the collection of expired air was continued for 15 minutes in order to observe the recovery curve.

TABLE 1.—CHANGES IN RESPIRATION AND BLOOD CHEMISTRY WITH SPONTANEOUS HYPERVENTILATION AND WITH HYPERVENTILATION CAUSED BY BREATHING 11% CARBON DIOXIDE.

(Subject: E. C. B., January 9, 1937.)

Time (min.).		Expired air, l per min.	Metabolism, % of basal	O_2 uptake, cc. per kg. per min.	% CO_2 in expired air.	% O_2 in expired air.	CO_2 expired, cc. per min.	% red blood cells in blood.	pHs at 38° C.	$(CO_2)b$, mM. per l.	pCO_2, mm. of Hg.	$(BHCO_3)s$, mM. per l.
End of interval.	Middle of interval.											
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)
Basal	0	4.18	100	3.22	3.61	16.67	149	0.41	7.39	21.36	41.1	24.2
1.55	0.78	18.46	205	6.66	2.90	18.69	535					
	1.00	...	...	...	...	...	...	0.41	7.45	20.46	34.9	23.5
2.58	2.07											
3.60	3.09	19.23	195	6.31	2.40	18.94	461					
5.73	4.67	17.69	171	5.54	2.15	19.06	380					
	5.00	...	...	...	...	...	...	0.41	7.53	19.33	28.0	22.7
7.78	6.75	15.55	167	5.42	2.13	18.90	331					
	7.60	...	...	...	...	...	...	0.41	7.55	19.77	27.4	23.1
9.97	8.87	14.14	165	5.35	2.18	18.76	308					
	9.50	...	...	...	...	...	...	0.41	7.50	18.93	29.1	22.1
10.00	Stop	Hyperventilation										
12.50	11.23	3.92	101	3.26	2.37	16.67	93					
	12.00	...	...	...	...	...	...	0.41	7.47	19.14	31.5	22.2
17.56	15.03	3.08	102	3.33	2.66	15.46	82					
	17.00	...	...	...	...	...	...	0.41	7.42	20.93	38.0	23.9
26.02	21.79	4.19	115	3.75	2.88	16.27	121					
	25.00	...	...	...	...	...	...	0.42	7.38	22.13	43.7	24.9
27.52	26.76				——	No sample	——					
	27.00	Start	Breathing		11% CO_2							
28.63	28.08	27.90	...	...	10.1							
29.38	29.01	45.36	...	...	10.5	...	...	0.42	7.18	25.30	65.8	23.7
	29.38	Stop	Breathing		11% CO_2							
31.01	30.20	21.08	149	4.84	4.28	18.99	902					
38.80	34.90	4.84	108	3.48	3.85	16.86	186					
45.21	42.02	4.80	107	3.47	3.66	16.88	176					

Basal Data.

BMR*	..	..	..	−0.39	−1.4	−4.1
Pulse rate	88	74	82	81	79	78
B.P.	114/84	114/81	113/83	101/81	110/80	112/79
Resp. rate	17	17	18			
Height	150.5 cm.					
Weight	57.4 kg.					
Age	27 years					

* Boothby-Sandiford norms.

Results. From Table 1 and Figure 1 it is evident that the respiratory volume increased from 4.1 to 19.23 liters per minute during the first 4 minutes of the period of overbreathing but decreased

somewhat during the last 6 minutes. The rise in the pH of the blood from 7.39 to 7.55, the fall in pCO_2 from 41 to 27 mm., and the slight but progressive decrease in the bicarbonate of the serum from 24.2 mM per liter (53.2 volumes %) to 22.1 mM per liter

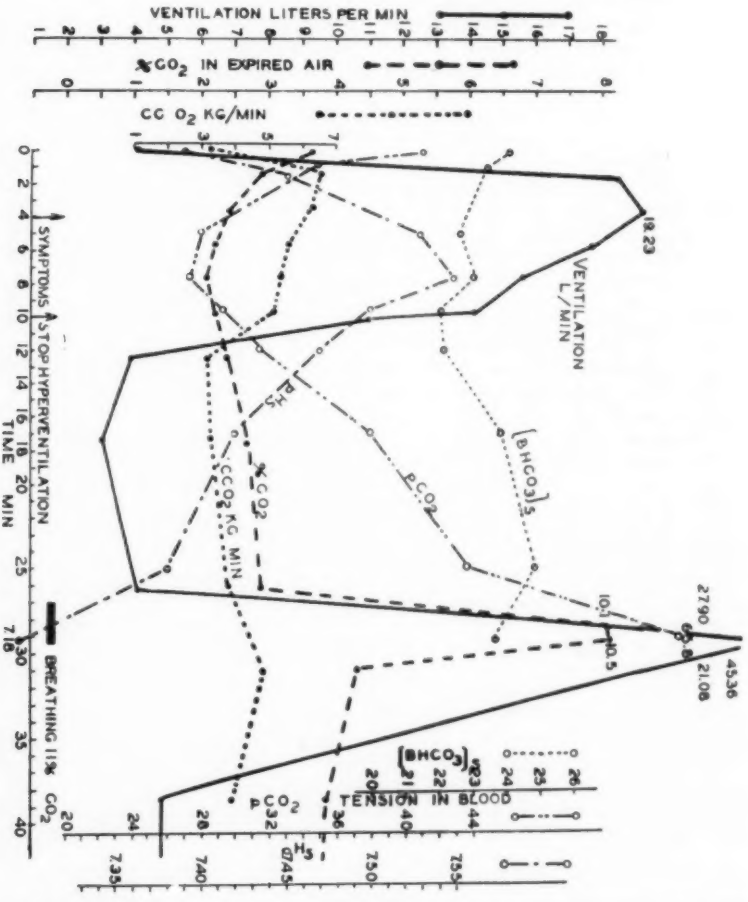

FIG. 1.—Changes in respiration and blood chemistry with hyperventilation and breathing 11% CO_2. ——— ventilation volume in liters per minute. – – – – – bicarbonate content of blood serum. —.—.— pH of blood serum. —..—..— CO_2 tension of arterial blood. ——— % CO_2 in expired air. ..... O_2 consumption measured as cc. of O_2 per kg. per minute.

(48.6 vol. %) are shown in Table 1. The symptoms of dizziness, fatigue, palpitation, constriction in the chest and throat and sense of "suffocation," headache, numbness of the hands and feet and finally frank tetany, began at the fourth minute and were fully established at the end of the fifth minute. The oxygen consump-

tion increased by 100% during the early part of the experiment. The CO_2 content of the expired air fell constantly (as is shown in the curve in Fig. 1) from 3.6 to 2.2%, but it should be noted that the total output of CO_2 increased from 149 to 308 cc. per minute. Hyperventilation was stopped at the tenth minute but the compensatory apnea which is marked in normal subjects[65] at the cessation of overbreathing was slight in this patient. The return of the pH of the blood was slower than in normal subjects, although practically complete in 15 minutes. Some of the symptoms were still present after 25 minutes, probably because of the slower restoration to normal of acid-base balance in the tissue fluids than in the blood. Twenty-seven minutes after the experiment started, a mixture of air with 11% CO_2 was administered, which increased the ventilation volume to 45.36 liters per minute, but at the same time relieved the headache, palpitation, precordial pain, paresthesias and muscle cramps. This high concentration of CO_2 was so uncomfortable for the patient that it was continued for only $2\frac{1}{2}$ minutes. After the patient had breathed CO_2 for 2 minutes, a blood sample was found to have a pH of 7.18 and a bicarbonate content of 23.7 mM per liter (52.14 volumes %).

The alterations in acid-base equilibrium are more readily visualized in Figure 2, in which the data have been plotted on tri-axial coördinates (Hastings and Shock[65]). In this chart pH lines run vertically, bicarbonate lines run from upper left to lower right, and CO_2 tension lines from upper right to lower left. All three scales intersect at 120 degrees and the bicarbonate and pCO_2 scales are logistic. This system provides maximal dissociation between respiratory and metabolic factors in acid-base equilibrium since it has been shown that CO_2 titration curves lie along the line "xy," and fixed acid changes take place along the line "AB" which is perpendicular to the respiratory line "xy." In Figure 2, the experimental points are numbered consecutively, and the path of displacement during 10 minutes of hyperventilation and the path during recovery are shown. Peters, Bulger, Eisenman and Lee,[56] Myers and Booher[53] and Hartmann and Smyth[33] have stated that tetany appears at a pH of 7.6 in normal individuals, but Hastings and Shock[65] noted symptoms of tetany in subjects when the pH was displaced to 7.55 by 15 to 20 minutes of hyperventilation. The patient, E. C. B., developed signs and symptoms of tetany after 5 minutes of hyperventilation when the pH reached 7.5, although at the onset of overbreathing the pH was normal. Furthermore, comparison with data on normal subjects[65] indicates that the patient's recovery was normal in direction but slow. From these data it is evident that she had symptoms of tetany before the pH had shifted as far toward the alkaline side as is necessary for the development of tetany in normal individuals, and that her recovery was slower than that of normal persons.

The displacement of the acid-base equilibrium by the breathing of 11% CO_2 for 2 minutes is shown in Figure 2 at point "A." The divergence of the path from the theoretical line "xy" is in all probability due to the short period of administration of CO_2, which caused a rapid rise in the pCO_2 without attainment of equilibrium

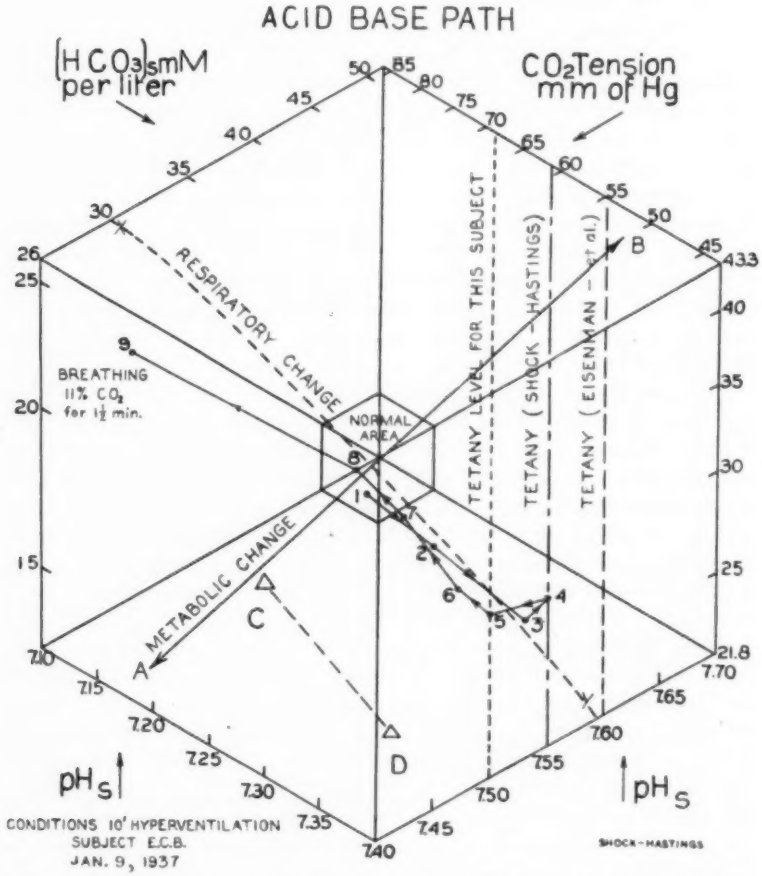

FIG. 2.—Change in acid-base balance of the blood produced by hyperventilation for 10 minutes in patient E. C. B. See text for explanation of coördinates.

of the bicarbonate content. Unfortunately, the CO_2 and air mixture had not been analyzed until after it was administered. A satisfactory mixture contains between 2 and 5% CO_2

Discussion. The symptoms of effort syndrome can be explained clearly when its relation to the hyperventilation syndrome is recognized. The symptomatology and the biochemical and physiologic

changes[1,3,6,8,9,11,14,16–20,22,23,25–29,34–37,39–41,44–47,49,51,52,54,57,58–60,63,64a,b,67–70,72a,b] which occur during hyperventilation have been reported adequately. It has been shown that the shift in the acid-base bal-

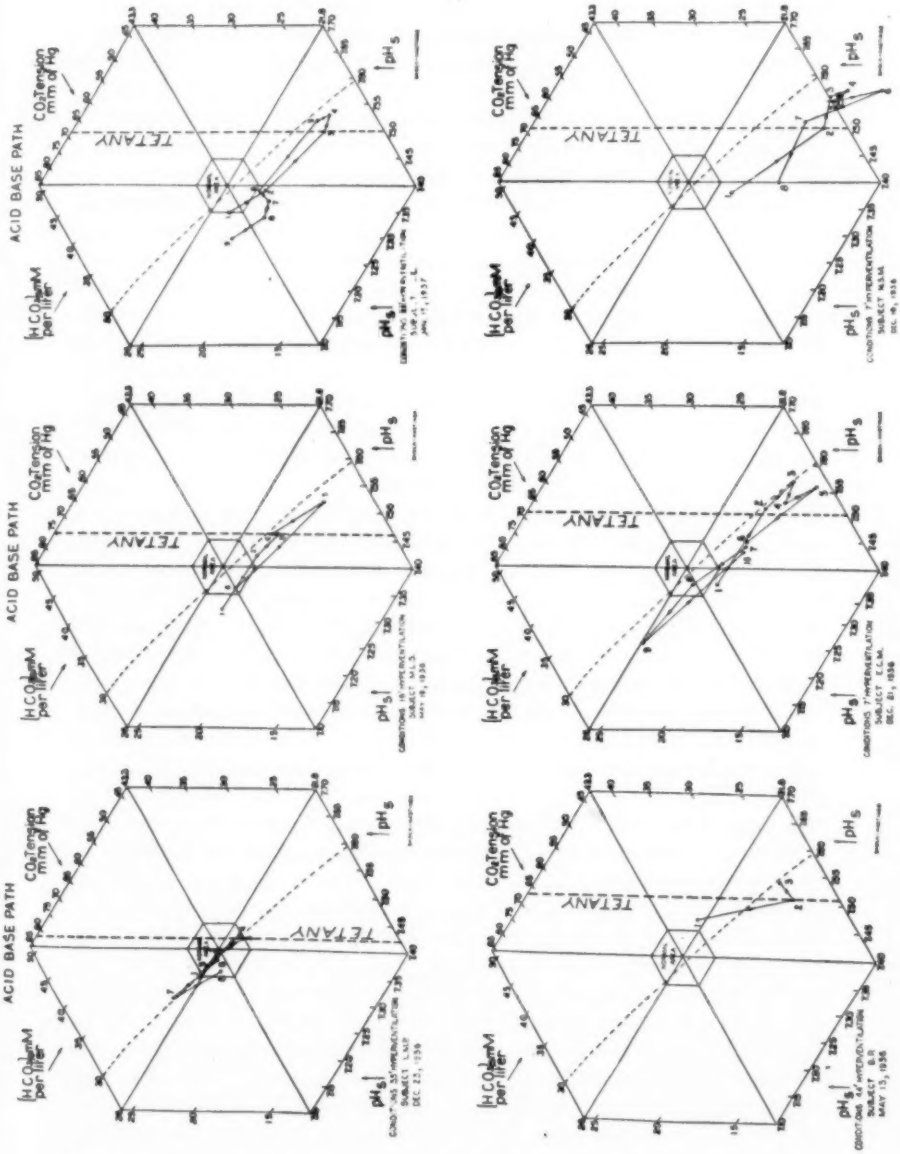

FIG. 3.—Alterations in acid-base balance of blood produced by hyperventilation in patients suffering from "effort syndrome." For explanation of coördinates see text.

ance toward the alkaline side, rather than any change in the calcium and phosphorus metabolism[16 26 28 55 65] is responsible for the symptoms. While hyperventilation may be caused by anoxemia,[21 24 31 62] organic nervous diseases,[5 32] hot baths and hyperthermia,[2 7 10 12 30 38 42] and anxiety and effort,[13 41 47 72b] we are most interested in the two causes last mentioned, since it has been recognized that the combination of anxiety and effort produces the symptoms listed variously under the diagnoses of "soldier's heart," disordered action of the heart (D.A.H.), "neurocirculatory asthenia" and "effort syndrome." Most of these symptoms require no further explanation but there are several points which need clarification.

The sense of suffocation is probably due to cerebral anoxemia. Increase in total oxygen consumption during overbreathing is not incompatible with cerebral anoxemia, since the latter is a local condition due to vasoconstriction. Cobb and Fremont-Smith[15] and Wolff and Lennox[73] have demonstrated that hyperpnea causes cerebral vasoconstriction. Mond and Wassermann[50] have stated that sighing respiration is one of the signs of cardiac dyspnea, presumably on the basis of cerebral anoxemia. Administration of carbon dioxide has been shown to relieve Cheyne-Stokes respiration, sighing and the sense of suffocation, probably by relieving cerebral vasoconstriction and consequently cerebral anoxemia.

Many of the patients with effort syndrome show periodic or suspirous breathing on the spirograms obtained during the determination of the basal metabolic rate by the Benedict-Roth apparatus and many patients are actually hyperventilating during the test. In our experimental work, the metabolic rate rose to levels of 100 to 180% above the basal level when the patients hyperventilated. Part of the increase in metabolism may be due to the muscular work of overbreathing, to alkalosis, to increased secretion of epinephrine or to combinations of these factors. But part of the effect is more apparent than real. When hyperventilation is begun, there is a washing out of alveolar air so that the CO_2 content of the expired air will be higher and the O_2 content will be lower than is normal. This lowered O_2 content will appear as an increase in O_2 consumption which is maximal during the early stages of hyperventilation. Conversely, when hyperventilation ceases, the O_2 content of alveolar air is appreciably higher than normal. Restoration of the normal alveolar O_2 concentration is brought about by the absorption of O_2 into the body from the alveolar air. Until the extra oxygen present in the alveoli is absorbed and a normal alveolar O_2 concentration is restored, analyses of the expired air will show a decrease in the amount of oxygen used. If we assume that the residual air represents alveolar air with an average value of 1 liter in normal subjects, then altering the oxygen concentration from 19.5 to 15% would make 45 cc. of oxygen available. If the basal oxygen consumption were 200 cc. per minute, the oxygen uptake

observed during the first minute following hyperventilation would be reduced by approximately 25%. Herxheimer and Kost[37] postulated that the decreased oxygen consumption following hyperventilation represents oxygen storage by some unknown mechanism within the body or by actual increase in oxidative efficiency resulting from preceding excessive ventilation. We believe, however, that the change in alveolar oxygen tension accounts for the apparent decrease in oxygen consumption.

We have been impressed by the peripheral vasoconstriction which is so marked during forced overbreathing that the fingers must be stabbed deeply to obtain blood for chemical studies. This has been noted previously by Schneider and Truesdell.[62] The vasoconstriction results in a lowered oxygen saturation which tends to minimize the extent of the measured respiratory alkalosis.[65] Undoubtedly, blood obtained by arterial puncture would show an even greater pH displacement than we have demonstrated in finger blood, because the latter must contain some tissue fluid not yet in equilibrium with the circulating blood.

It must be made clear that the shift in acid-base equilibrium produced by hyperventilation is along the respiratory axis, line "xy" in Figure 2. This type of displacement involves changes in pCO_2 and pH primarily. Inspiration of CO_2 will alleviate the symptoms by replacing the CO_2 lost by overbreathing and the pCO_2 and pH values will return to normal along the same "respiratory axis" in the reverse direction. Previous experiments[65] have shown that changes of this kind take place very rapidly. The pH can be shifted toward the alkaline side also by displacing the acid-base equilibrium along the "metabolic axis" graphed as line "AB" in Figure 2. The administration of acids or such acidifying salts as NH_4Cl and $CaCl_2$ will prevent the symptoms in patients who hyperventilate because the pH is on the acid side (point "C" in Fig. 2) before they begin to overbreathe. Consequently, even though the pH is displaced to the same extent (to point "D" in Fig. 2), the level at which tetany appears is not reached. Thus the apparent anomaly of producing a metabolic shift as therapy for a respiratory shift is explained.

Fortified with a knowledge of the etiology of effort syndrome, we are now in a position to treat this condition rationally. An impressive method of approach to the patient is to have him hyperventilate to the point of production of symptoms and then have him continue to overbreathe air to which 2 to 5% CO_2 has been added (a tank of the gas mixture connected to the usual anesthetic bag and mask may be used). The CO_2 mixture relieves the symptoms within 15 to 30 seconds. When the patient realizes that the doctor understands the cause of his trouble, the first hurdle in treatment is passed.

The next step is to prescribe measures which will prevent over-

breathing or counteract the resulting alkalosis when overbreathing has occurred. The patient may be taught to breathe abdominally so that, even though the respiratory rate increases, the total ventilation is far less than it would be either with chest breathing or with chest and abdominal breathing combined. Sedatives may be prescribed to raise the patient's threshold of sensitivity to all stimuli. Ammonium chloride in doses up to 45 grains a day will tend to produce an acidosis, so that even though the patient hyperventilates to the same degree as previously, the pH will not be shifted to the point of tetany. Since so many of these patients have gastric anacidity, hydrochloric acid may be added to help in the production of acidosis. It should be stressed that, in sufferers from anxiety states complicated by the hyperventilation syndrome, treatment with sedatives, acidifying drugs and diets is merely a temporary measure to carry the patients along comfortably while psychiatric investigation of the anxiety is undertaken. The general practitioner or internist may be able to discover and relieve the anxiety although in many cases study by a competent psychiatrist is required.

The old terminology of effort syndrome should be discarded and a more descriptive term employed expressive of its etiology. Thus the diagnosis might be "anxiety state with (or complicated by) the hyperventilation syndrome." Such a diagnosis is commonly used to describe this condition in the records of the University of California Hospital.

Conclusion. The respiratory alkalosis resulting from hyperventilation produces the symptoms of effort syndrome.

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CIGARETTE SMOKING.

I. As a Cause of Fatigue; II. Effect on the Electrocardiogram With and Without the Use of Filters.

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It is a generally established fact that tobacco smoking may have deleterious results that seem to be overshadowed by the greater momentary pleasurable effects. Its use definitely becomes a habit[8,13] which is discontinued only with more or less difficulty. As a result, many of us have accepted it as a matter of fact and frequently do

not carefully consider the effect of smoking on the symptomatology of our patients.

This study began as a result of the unsuccessful treatment of 2 patients who complained of fatigue. Both suffered mainly from this symptom for a number of years. All sorts of medication had been of no avail. One of these patients noted that his pulse rate increased considerably every time he smoked a cigarette. As a result of this the question of tobacco as the cause of the fatigue arose. Both patients improved and gained weight after cessation of smoking.

TABLE 1.—CASES OF FATIGUE RELIEVED BY CESSATION OF CIGARETTE SMOKING.

Case.	Sex.	Age.	History.	No. of cigarettes daily.	Effect of cigarette smoking on the heart rate.		Condition after cessation of smoking.
					Before smoking.	After smoking.	
W. C.	M	37	Extremely tired past 3 years. Pains left chest. No relief from sedatives or thyroid extract.	20	80	100	Patient gained 10 pounds; felt greatly improved. Was not tired.
E. S.	F	23	Tired past year. Loss of weight.	10–15	80	125	Gained 4 pounds in 3 weeks. Not tired.
H. S.	M	30	Tired past year.	20	66	100	In a few weeks increased energy.
H. H.	M	26	Exhausted all the time. Nervous past 1½ years.	30–40	90	108	In 2 weeks felt well; gained weight.
N. S.	F	21	Tired most of the day.	10–15	100	140	In 3 weeks felt well; gained 5 pounds.
B. R.	M	45	Fatigue. No relief from tonsillectomy, sedatives, tonics.	25	84	102	In 2 weeks increase in energy; gained 5 pounds.

In addition to these 2, 4 other patients whose main symptom was a tired feeling were relieved by stopping tobacco (Table 1). It is not meant to convey the impression that all patients who are tired and who smoke are improved by discontinuing the smoking. It is only meant to emphasize the point that there are people in whom fatigue is the result of cigarette smoking.

This brings up the question as to the products of tobacco smoke which are harmful to the system and especially what part of the smoke produces the general effects such as fatigue.

Dixon,[8] in a very exhaustive study of tobacco smoke, has shown that the main constituents of the tobacco smoke are pyridine and its bases, ammonia, carbon monoxide and nicotine. Other substances present in traces are cyanides and sulphocyanides. Arsenic is present in American tobaccos in amounts many times greater than those permitted in foods.

A *B*

FIG. 1.—*A*, Zeuss type of filter holder. Cigarette used as the filter. *B*, Denicotea type of filter holder. Cartridge containing silica gel used as the filter.

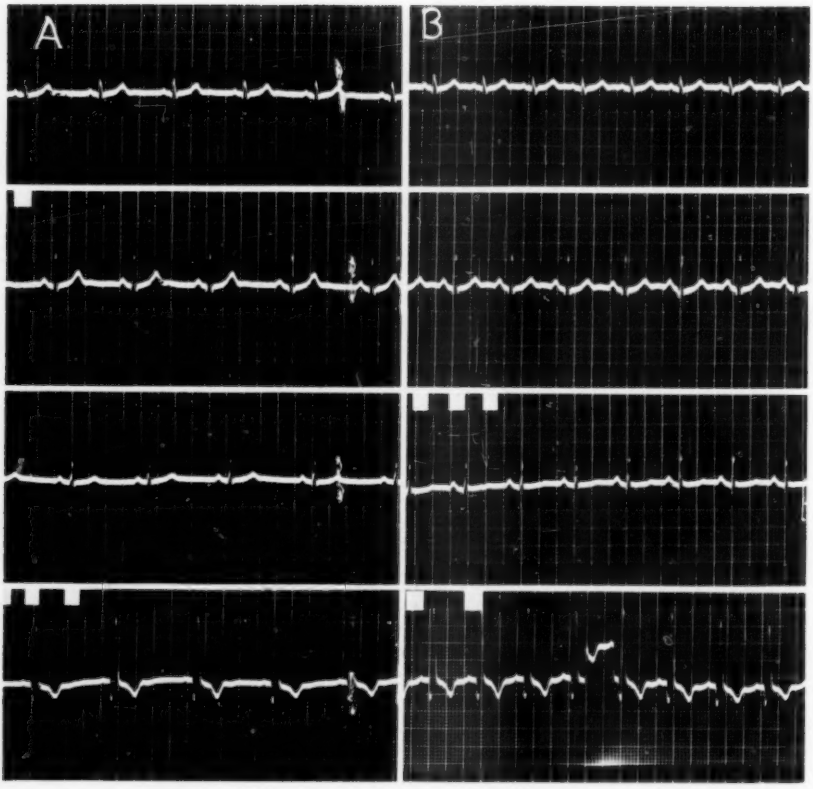

FIG. 2.—*A*, Electrocardiogram before smoking. *B*, Electrocardiogram after smoking one-half of a standard cigarette. Major effects, heart rate increased from 70 to 100; height of *T* waves decreased.

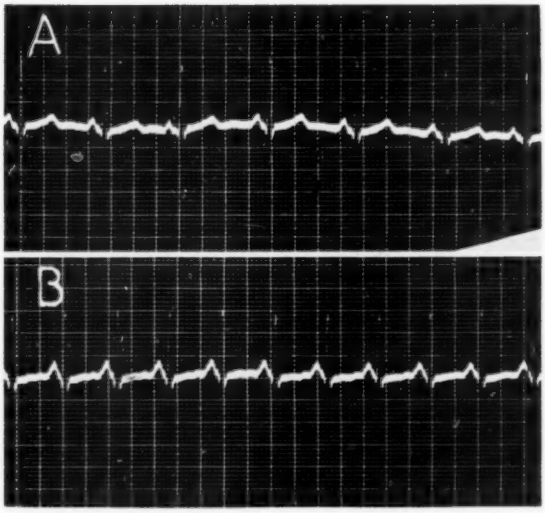

FIG. 3.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a standard cigarette with the Zeuss filter. Major effects, heart rate increased from 100 to 130; *T* waves isoelectric.

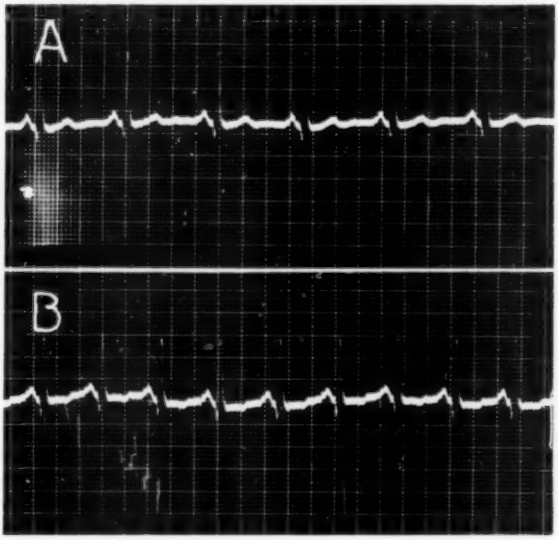

FIG. 4.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a standard brand cigarette with the Denicotea filter. Major effects, heart rate increased from 84 to 120; height of *T* waves decreased.

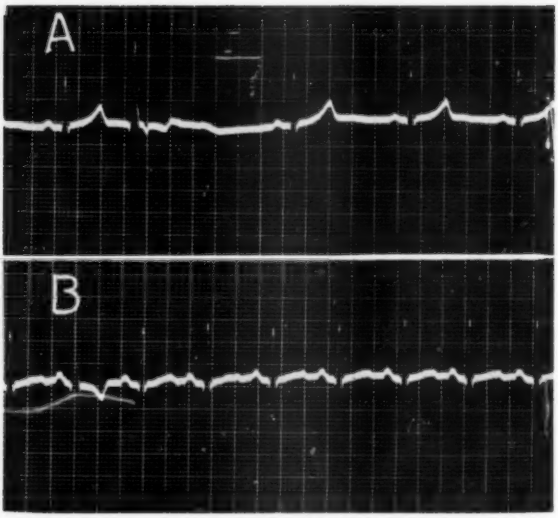

FIG. 5

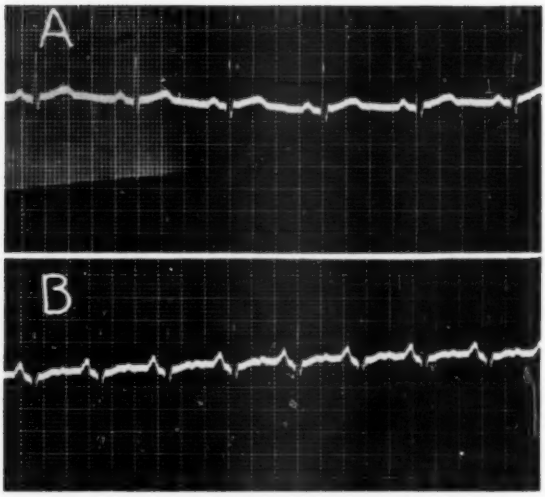

FIG. 6

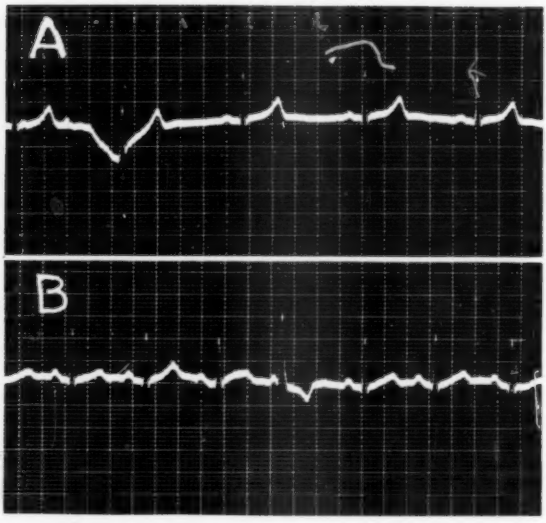

FIG. 7

He divided the effects of tobacco smoke upon the body into local and general. The ammonia gas and pyridine or pyridine derivatives produce the symptoms because of their irritation of mucous surfaces. It is these substances that cause the morning cough, the irritation of the throat and tongue, and conjunctivitis. He has shown that carbon monoxide and nicotine are the substances that can be absorbed into the circulation by way of the respiratory tract and it is these that can produce the general or systemic effect.

Cigarette smoke yields from 0.5 to 1% of carbon monoxide. The smoke from a pipe yields 1%, and that from a cigar 6 to 8%. The tobacco smoke reaches the mouth freely diluted with air and the amount of carbon monoxide absorbed in the mouth is negligible, so that pipe or cigar smokers who do not inhale have little to fear from carbon monoxide. Baumberger[5a] has computed that cigarette smoke as it reaches the mouth may contain as much as 7.2 to 25 parts of carbon monoxide in 10,000 parts of air. This smoke if inhaled for 1 hour at the rate of 5 puffs a minute, theoretically could be enough to saturate the blood with 22% of carbon monoxide. But smokers do not habitually inhale as often or as continuously as this and Baumberger believes that it is extremely unlikely for the carbon monoxide to reach a sufficient saturation to produce any injurious effect in the average smoker. Thus by and large the systemic effect of carbon monoxide in tobacco smoke is negligible.

This leaves nicotine, the most important constituent of tobacco smoke, to produce a systemic effect. Various investigators[8,11,14,19,20] have shown that nicotine is the substance that produces the general reaction from smoking. These general effects of nicotine will result in a rise in pulse rate, blood pressure and decrease in skin temperature. Realizing that nicotine is the harmful element in cigarette smoke and that in most people the habit is difficult to stop, the question arose as to the least harmful way of smoking.

At this time two filter holders appeared on the market, called Zeuss and Denicotea (Fig. 1), the use of which were supposed to remove a large percentage of the nicotine as well as the irritant products of cigarette smoke. It was wondered whether such filters would be effective in removing the nicotine effect and thus the harmful result of smoking.

For purposes of this study it was thought that some of the effects of the nicotine in the tobacco smoke could be best recorded by the electrocardiogram. The change in heart rate has been shown to be one of the most characteristic reactions of the nicotine of tobacco smoke and the electrocardiogram offers a permanent record. At the same time any other effect that smoking may produce on the electrocardiogram could be studied.

Method. The subjects tested did not smoke after the previous night. After resting comfortably in a chair, standard electrocardiograph tracings were taken before and after smoking one-half of the cigarette. It was noted

that the effect would occur within a minute after beginning to smoke, *i. e.*, even before one-quarter of the cigarette was consumed. As it was also observed that the information desired could be obtained for all practical purposes from the comparisons of Leads II before and after smoking, this was the lead that was studied in most of the tests. With this technique tracings were taken before and after smoking standard and denicotinized brands of cigarettes. Then on different days or with different subjects using the same technique the effect of smoking the same kind of cigarettes with a holder containing a filter was noted. The observation whether the subject puffed or inhaled was also made.

The filters used in this study, as already stated, are on the market under the name of Zeuss and Denicotea (Fig. 1). The Zeuss Filter-Holder consists of an aluminum tube in which a cigarette is placed to act as a filter. The Zeuss corporation claim that over 70% of the nicotine and tar are removed from the cigarette smoke by this method. In addition, they tell you to smoke all you like.

The Denicotea Filter-Holder consists of a tube in which is inserted a cartridge containing a silica gel to act as the filter. This filter has been examined by the Chemical Laboratory of the American Medical Association[1b] and their report has shown the presence of silicic acid in the granular material in the filter. After smoking, qualitative tests of the filter have revealed the presence of nicotine, traces of cyanides. pyridines and resinous material. Their conclusions are that this filter removes 60% of the nicotine from the cigarette smoke and that its efficiency decreases with its use. Cyanides, pyridine and some of the resinous material also are removed from the smoke by this filter.

TABLE 2.—THE EFFECT OF CIGARETTE SMOKING ON LEAD II OF THE ELECTROCARDIOGRAM.

Age groups.	No. of tests.	Sex.		Increase in heart rate.			Decrease in height of *T* wave in millimeters in Lead II.		
		M.	F.	No. tests with no increase.	Highest.	Aver.	No. tests with no decrease.	Lowest.	Aver.
17–35 . . .	44	14	30	3	50	21	10	3	0.78
35–50 . . .	9	5	4	2	40	18	7	1	0.51
50–on . . .	11	6	5	7	16	4	8	0.75	0.12
Total . . .	64	25	39	12	..	..	25		

Data. Table 2 is a summary of the effect of smoking cigarettes on Lead II of the electrocardiogram. There were 64 tests made, 25 males and 39 females. These 64 subjects were divided into three age groups; the young consisted of subjects between the ages of 17 and 35; the middle age group between the ages of 35 and 50; the old age group from 50 upwards. The number of cases with no change in heart rate, the maximum and average increase in heart rate as well as changes in the *T* wave were recorded. In the young group there were 44 tests, only 3 of whom had no increase in heart rate after smoking. The highest increase in rate was 50 per minute; the average for this group was 21.

In this same group, changes in the *T* wave took place in 34 of the 44 subjects, the greatest drop was 3 mm. and the average was 0.78 mm.

In the middle age group the figures were comparable, but in the group over 50 years of age there was no increase in heart rate in 7 out of the 11 tested; the highest increase was 16 and the average increase was only 4 beats per minute. Likewise changes in the *T* wave were less significant.

TABLE 3.—COMPARISON OF THE EFFECT OF SMOKING STANDARD AND SO-CALLED DENICOTINIZED BRANDS OF CIGARETTES ON LEAD II OF THE ELECTROCARDIOGRAM.

Age group.	Standard brands.									Denicotinized brands.								
	Total No. of tests.	Sex.		Increase of heart rate.			Decrease of height of *T* in Lead II.			Total No. of tests.	Sex.		Increase of heart rate.			Decrease of height of *T* in Lead II.		
		Male.	Female.	No. tests with no change.	Highest.	Average.	No. tests with no change.	Lowest.	Average.		Male.	Female.	No. tests with no change.	Highest.	Average.	No. tests with no change.	Lowest.	Average.
17–35	27	11	16	3	45	23	7	3.0	0.65	17	3	14	0	50	16	3	3.0	0.69
35–50	8	5	3	2	38	17	5	1.0	0.15	1	0	1						
50–on	10	5	5	6	16	4	7	0	0	1	1	0						
Total	45	21	24	..	..	..	..	..	...	19	4	15						

Table 3 is a comparison of the results obtained from the standard brands of cigarettes in which the nicotine contents averages about 2% as against the so-called denicotinized brands in which the nicotine content has been estimated to give an average of about a little less than 1%.[1] The standard brands of cigarettes mainly used were Chesterfield, Camel and Lucky Strikes. The denicotinized brands consisted of Sano and Carl Henry.

In the young group, there were 27 tests with standard brands as compared with 17 subjects in the denicotinized brands. Three of the subjects smoking standard brands failed to get a rise in heart rate while every one of the 17 tests in the denicotinized group had a rise in rate. The highest rise in the heart rate was 45 in the standard brands as compared to 50 in the denicotinized. The average was 23 in the former as compared to 16 in the latter. *T* wave changes were comparable in both types of cigarettes. Not enough tests were made in the older groups to be of any significance.

Table 4 is a chart comparing the effects of smoking cigarettes of both brands without a filter as compared to smoking with both the Zeuss and Denicotea types of filters. Here the results in people under 50 are compared. Briefly, the standard brands with no

filters showed an increase in the heart rate in 14 of the 18 subjects tested as compared to an increase in the rate in all cases with the Zeuss filter and an increase in 7 of the 8 subjects smoking with a Denicotea filter.

The findings are comparable for the changes in the *T* waves and more details can be obtained from studying the tables.

TABLE 4.—COMPARISON OF SMOKING STANDARD AND SO-CALLED DENICOTINIZED CIGARETTES WITH AND WITHOUT FILTERS ON LEAD II OF THE ELECTROCARDIOGRAM.

Age group:	Standard brands.									Denicotinized brands.								
	No filter.			Zeuss filter.			Denicotea filter.			No filter.			Zeuss filter.			Denicotea filter.		
	17–35 yrs.	35–50 yrs.	Total.	17–35 yrs.	35–50 yrs.	Total.	17–35 yrs.	35–50 yrs.	Total.	17–35 yrs.	35–50 yrs.	Total.	17–35 yrs.	35–50 yrs.	Total.	17–35 yrs.	35–50 yrs.	Total.
No. of tests	14	4	18	6	3	9	7	1	8	3	1	4	10	0	10	4	0	4
No. of tests with no increase in heart rate	3	1	4	0	0	0	0	0	0	0	0	0	1	..	1	1	..	1
Highest increase in heart rate	40	38	40	45	18	45	40	30	40	50	36	50	30	..	30	30	..	30
Average increase in heart rate	19	14	16	30	15	25	24	34	21	22	36	21	13	..	13	17	..	17
No. of tests with no decrease in height of *T* wave	5	3	..	2	2	4	3	..	3	1	1	2	4	..	4	1	..	1
Lowest decrease in height of *T* wave	1.5	0.5	..	3.0	0.5	3	1.5	..	1.5	3.0	..	3.0	3.5	..	3.5	1.25	..	1.25
Average decrease in height of *T* wave	0.42	0.12	..	1.12	0.16	0.91	0.57	..	0.50	1.33	..	0.8	0.55	..	0.55	0.56	..	0.56

TABLE 5.—COMPARISON OF THE EFFECT ON THE ELECTROCARDIOGRAM OF INHALING VERSUS PUFFING IN CIGARETTE SMOKING IN PEOPLE UNDER FIFTY.

		Increase in heart rate.			Decrease in height of *T* wave.		
	No. tests.	No. tests with no change.	Highest.	Average.	No. tests with no change.	Lowest.	Average.
Inhale	59	4	50	19	22	3.0	0.64
Puff	5	2	20	4	3	0.5	0.20

Table 5 demonstrates the effect of inhaling *versus* just puffing. In the latter, only the mucous membrane of the mouth is available for absorption. From this table it can be readily seen that most of the cigarette smokers inhaled. The 5 that puffed had an increase in pulse rate in 3 cases, the highest being 20 as compared to 50 in those who inhaled, with an average rate increase of 4 as compared to 19 in the subjects who inhaled.

Figures 2 through 7 demonstrate the effect of inhaling cigarette smoke on Lead II of the electrocardiogram. Figure 2 also shows the effect on the other leads.

Figure 2 represents the 4 leads of the electrocardiogram taken after smoking one-half of a standard brand of cigarette. The heart rate has increased from 80 to 100 and the *T* wave has dropped 1 mm.

Figure 3 shows Lead II before and after smoking one-half of a standard brand of cigarette with the use of a Zeuss filter. Here the rate has increased from 100 to 130 and the *T* wave has become flat. This figure also shows one of the minor and less consistent changes, namely, a slight increase in the height of the *P* wave.

Figure 4 reveals Lead II before and after smoking one-half of a standard brand of cigarette with the use of a Denicotea filter. These leads show a rise in heart rate from 84 to 120 and a flattening of the *T* wave. One of the minor changes also noted is a decrease in the amplitude of the *QRS* complex.

Figure 5 represents Lead II taken before and after smoking one-half of a denicotinized brand of cigarette. The heart rate has increased from 70 to 110, the *T* wave has decreased about 3 mm. A minor change here is the increase in the height of the *P* wave and the amplitude of the *QRS* complex.

Figure 6 shows the effect of smoking a denicotinized cigarette with a Zeuss filter. The heart rate has increased from 70 to 110, and the *T* wave has become isoelectric. The *P* wave has increased about 1 mm.

Figure 7 demonstrates the effect of smoking one-half of a denicotinized brand of cigarette with a Denicotea type of filter. The heart rate has increased from 60 to 100 and the *T* wave has dropped 3 mm. The *P* wave is slightly more prominent after smoking.

These figures definitely show increases in heart rate and lowering of the *T* waves as well as minor changes in the *P* waves and amplitude of the *QRS* complex after smoking standard and denicotinized brands of cigarettes. It is readily seen that similar results occurred with both brands of cigarettes with and without the use of filters.

Discussion. Dixon,[8] as already mentioned, has reviewed the whole tobacco question and Bastedo[2] more recently has mentioned the various systemic symptoms that can result from smoking. The evidence that the nicotine of the tobacco smoke is the cause of these symptoms has been proved by numerous studies.[8,11,14,20] Baumberger[3b,c] in 1923 has demonstrated that the nicotine content of cigarette smoke is about 0.57% of the weight of the cigarette tobacco; 14 to 33% of this nicotine appears in the smoke puffed. He further has shown that 66.7% of the smoke and presumably the nicotine is retained in the body in puffing, while 88.2% is retained in inhaling. Maddock and Coller,[14] stating that a standard brand of cigarette contains about 1 gm. of tobacco and that about 2.2% of this is nicotine, have calculated that in puffing two-thirds of a cigarette the body will absorb 2.52 mg. of nicotine and that in inhaling the same amount of cigarette smoke, 3.33 mg. of nicotine will be absorbed. The intravenous injection of 1 mg. of nicotine will produce

an increase in blood pressure, pulse rate and decrease in the skin temperature of the fingers and toes.[14] On smoking a cigarette these same effects will occur. Thus these results following smoking is due to nicotine.

Tournade, Chevillot and Bernot,[19] by comparing the effect of nicotine and the inhalation of tobacco smoke on denervated tongue muscle, also have shown that nicotine is the substance present in the tobacco smoke that causes the systemic effects.

The effect of tobacco smoking on the electrocardiogram has been reviewed recently by Graybiel, Starr and White.[9] They mention the studies of Bull, Clerc and Pezzi,[6] and Mattioli[15] who studied the effect of nicotine in animals by the use of the electrocardiogram. The former workers observed nodal rhythm, auricular flutter and heart block after the injection of toxic doses of nicotine in dogs and rabbits.

Ssalischtscheff and Tschernogoroff[17a,b] also reviewed by Graybiel and his collaborators,[9] were the first to analyze the effect of inhaling tobacco smoke on the human electrocardiogram. In their first article[17a] they worked with rabbits under ether narcosis and they noted that it required the injection of 0.1 mg. of nicotine to produce a slowing of the rhythm. In their work on humans[17b] they took electrocardiograms every 5 to 10 minutes until toxic symptoms of smoking occurred. They found that at the height of intoxication the heart rate was accelerated except in 1 instance. In most of their cases the form and height of the electrocardiogram did not change with the toxic symptoms from smoking.

Graybiel, Starr and White[9] noted in their study that after smoking a cigarette, or after toxic symptoms such as dizziness appeared, there was an average increase in heart rate of 13 a minute and that lowering or inversion of the *T* waves took place in 15 of the 45 subjects tested. Minor changes occurred in the *P–R* interval and the amplitude of the *QRS* complex in a few cases. They noted that full atropinization produced changes in the electrocardiogram similar to those from smoking.

Knowing that cigarette smoke may produce an increase in the heart rate as well as a decrease of the *T* wave and other minor changes in the electrocardiogram and knowing that nicotine is the factor in the cigarette smoke that produces these effects, we are justified in using the electrocardiogram to determine the efficiency of filters in removing the nicotine effect of smoking various brands of cigarettes.

In our study, it has been conclusively shown that smoking one-half of a cigarette produces a definite effect on the electrocardiogram in a large majority of subjects under 50; and that this effect was mainly registered by an increase in the heart rate and a decrease in the height of the *T* waves. In some cases there were an increase

in the height of the *P* wave and minor changes in the amplitudes of the *QRS* complex.

From studying the charts in similar age groups the effect from smoking standard and denicotinized cigarettes is very similar both in increase in rate and in lowering of the *T* waves. Again, smoking with the use of a filter produces the same effect on the electrocardiogram as the unfiltered smoke.

What is the significance of all this?

First, it seems that people under 50 reacted almost consistently to cigarette smoking as far as the heart rate goes. Those over 50 responded to a lesser degree if at all to cigarette smoking.

The action of nicotine is one of stimulation of the entire nervous system and this is followed by depression. The time the stimulation lasts usually coincides with the absorption of the nicotine, that is, with the period of active smoking. The stimulation of the sympathetic causes contraction of the arteries as shown by a decrease in skin temperature.[14] Contraction of the arteries alone can be the cause of the increased heart rate in order to obtain the same volume output per minute although direct action on the sympathetic to the heart may play the main part in the increased rate.

In people over 50 the arteries may not be elastic enough to respond to this stimulation, or the mucous membrane of the respiratory tract in the older people may not absorb the nicotine as readily. This point could be determined by the comparison of the effect of nicotine injected intravenously and that from smoking. Another point noted was that the 3 subjects in the group under 50 who failed to respond were not totally normal people. One had an essential hypertension, one ulcerative colitis and one mucous type of colon with achlorhydria. This may point to the fact that in the case of hypertension, overactivity of the sympathetic nervous system was already present. In the latter 2 cases it may be due to poor absorbability of the mucous membranes. These points will be elucidated by further study of such cases.

Sharlit[16] in 1935 suggested that a filter could remove the combustion products from the smoke stream and believed that such a substance was available but did not mention the name. By this method he suggested that the health hazard of cigarette smoking could be removed. Apparently the present filters on the market, notably the Zeuss and Denicotea types already described, do filter out a large percentage of nicotine as well as the substances that produce local irritation. But this study shows there is still enough nicotine in the filtered smoke that enters the mouth to produce a definite nicotine reaction. Although these filters are probably valuable by removing a part of the products that cause the local irritation of smoking, they have very little or no value in avoiding that which produces the systemic and habit effect of smoking,

namely the effect of nicotine. It may be suggested that although some nicotine gets through the filters, there is less nicotine to produce harmful effects. But the answer to this is that nicotine is a very toxic drug and it only requires 1 mg. to produce the specific effect. If in inhaling the smoke of two-thirds of a cigarette 3.33 mg. of nicotine are absorbed,[14] there still will be absorbed about 1 mg. of nicotine even after 70% of this nicotine is removed by a filter. But as the American Medical Association[15] report shows 60% is the highest efficiency of the new cartilage in the Denicotea filter and it decreases with each smoke, more than 1 mg. will be absorbed with this filter; more than is required to get a systemic effect. Even puffing, as tested with 2 people using a Zeuss filter, allowed enough nicotine into the mouth to get an increase in the heart rate. This demonstrated how readily nicotine causes these responses.

What is the mechanism that produced the fatigue from cigarette smoking? Although Dill and his collaborators[7] have reported that smoking 1 cigarette produces no change in the blood sugar the consensus of workers indicates that cigarette smoking produces a rise in blood sugar.[10,13,18]

McCormick[13] believes that the rise in blood sugar due to smoking is a protective mechanism as it occurs after morphine, strychnine and other drugs, as well as in infectious diseases. This rise in blood sugar depletes the glycogen stored in the muscles and this depletion represents a loss of potential muscular energy. Thus it can be readily seen that repeated cigarette smoking continues to deplete this muscle glycogen leaving a fatigued individual. He gives definite experimental evidence to prove this point. That smoking can cause fatigue has been shown by Baumberger and co-workers[4,5] who mention Lee's experience.[12]

The changes in *T* wave in the electrocardiograms observed from smoking in this study do not necessarily mean that there is coronary insufficiency but probably represents a reaction of the heart to increased work, as suggested by Graybiel and collaborators.[9] Even though these changes do not mean coronary spasm, yet the increased heart action, without the benefit to the body as a whole that healthful exercise produces, can do no good and probably does harm over a period of time.

LEGENDS FOR FIGS. 5, 6 AND 7.

FIG. 5.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a denicotinized cigarette. Major effects, heart rate increased from 70 to 110; height of *T* waves decreased 3 mm.

FIG. 6.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a denicotinized cigarette with the Zeuss filter. Major effects, heart rate increased from 70 to 110; height of *T* waves lowered 1 mm.

FIG. 7.—*A*, Lead II before smoking. *B*, Lead II after smoking one-half of a denicotinized cigarette with the Denicotea filter. Major effects, heart rate increased from 60 to 100; height of *T* waves decreased 3 mm.

Summary. 1. Six cases, whose main symptom was a fatigue that was relieved by discontinuing smoking, are summarized. The mechanism of the cause of fatigue is discussed.

2. The effect of smoking standard and denicotinized cigarettes with and without filters on Lead II of the electrocardiogram is demonstrated and discussed.

Conclusions. Cigarette smoking can be the cause of fatigue in some people and this fatigue can be relieved by stopping cigarette smoking.

Cigarette smoking produces definite changes in the electrocardiogram, mainly: *a*, An increase in the heart rate; *b*, a lowering of the *T* wave.

Both standard and the so-called denicotinized brands produce the same effects.

Although the filter-holders described decrease the amount of nicotine in cigarette smoke, a sufficient amount of nicotine is still available to produce the above changes in the electrocardiogram.

These effects occur mainly in people under 50 years of age.

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BOOK REVIEWS AND NOTICES.

THE TROUBLED MIND. A Study of Nervous and Mental Diseases. By C. S. BLUEMEL, M.A., M.D., F.R.C.P., M.R.C.S. (ENG.). Pp. 520. Baltimore: The Williams & Wilkins Company, 1938. Price, $3.50.

IN plain language, the author discusses such ramifications as neuro-psychiatry may have in the realms of religion, crime, business, advertising, politics, peace and war, together with some original theories pertaining thereto; and that is a rather large order. The subject-matter is considered under the following headings: Fixed ideas and reactions; psychoneurosis—its manifestations; psychoneurosis—its nature and causes; traumatic hysteria; clinical types of inhibition; sundry disorders; mental illnesses; closing comments. Many short histories well illustrate the differences between harmless mental subjects and those that are public disturbers.

Nearly half of the space is devoted to manifestations, nature and causes of the psychoneuroses; that is, those functional nervous disorders characterized by emotional and physical disturbances. Their "therapy may include such technique as persuasion, suggestion, desensitization, psychocatharsis, hypnosis, psychoanalysis, distributive analysis, unconditioning, and so on; . . . the objective is that of establishing emotional flexibility." There are minor errors, such as, traumatic hysteria which should be post-traumatic hysteria; that severe melancholia is closely allied to dementia precox is an opinion not usually held; nor is there "softening of the brain" in paresis. Being free from commercialism and unnecessary sex discussions, this wholesome book may be recommended to the lay reader. The bibliography is scant, a glossary is appended and there is an informative index.

N. Y.

RECENT ADVANCES IN PATHOLOGY. By GEOFFREY HADFIELD, M.D., F.R.C.P. (LOND.), Professor of Pathology in the University of London; Pathologist to St. Bartholomew's Hospital, etc., and LAWRENCE P. GARROD, M.A., M.D., B.CH. (CAMB.), F.R.C.P. (LOND.), Professor of Bacteriology in the University of London; Bacteriologist to St. Bartholomew's Hospital, etc. Pp. 420; 65 illustrations. Third Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1938. Price, $5.00.

Now that the volumes of this useful series are appearing in various editions, it should be noted that a later edition does not bring merely the knowledge acquired since the previous edition, as in a Year Book; but that it is a revised version of the earlier edition. Thus in this volume "little more than half of the previous text is retained. The first chapter is entirely new, and deals with two aspects of the fundamental problem of resistance to infection. One of these is concerned with the nature and significance of bacterial allergy, and adequate treatment of this subject has also necessitated re-writing sections on the pathogenesis of rheumatic fever, lobar pneumonia and glomerulonephritis. In the third chapter, which is also entirely new, we have stressed the striking potentialities of undifferentiated mesenchyme and have attempted to summarize present knowledge with regard to the reticuloses and the reticulo-sarcomata. Other chapters in which there are extensive alterations are those on deficiency diseases and on cancer. . . . Extensive additions have also been necessary in connection with subjects of silicosis, gastritis, the relationships between gastro-intestinal

function and anemia, and disorders of the adrenal and pituitary glands. In order to make further room for new matter, two chapters and five sections on subsidiary subjects have been omitted, as has a good deal of introductory matter originally designed to enable the reader to view the subject in its proper relationship to others. Only those who have attempted the compilation of a work of this scope and function can appreciate the difficulty of deciding what to include and what to omit." Nevertheless, with due regard for the differences in British and American requirements, we believe that the authors have acquited themselves well. E. K.

A General Textbook of Nursing. A Comprehensive Guide to the Final State Examinations. By Evelyn C. Pearce, Sister Tutor, The Middlesex Hospital, etc. Pp. 888; 176 illustrations. New York: E. P. Dutton & Co., 1938. Price, $3.75.

This book is written to serve as an introduction to nursing for the student nurse. Though written simply and briefly, nothing is sacrificed that would be of value to the student as she travels from one department to another in the hospital.

In many treatments administered by doctors, just what is expected to occur is described graphically, in order that the nurse may see the reason for supplying necessary equipment. It is interesting to discover the use of different materials. For instance one learns that salt may be used on ice for ice bags; small ice packs can be made of gutta percha; tow may be used for wash cloths. In England wool and tow take the place of our cotton. The measuring system is more exact—one computes dosage on the basis of 110 minims to 100 grains. Many unfamiliar terms are used and it will add considerably to one's vocabulatory if a dictionary is handy.

One thing that might be added to the book is a paragraph or more on artificial respiration. Neither the respirator that we use in the treatment of respiratory paralysis nor the use of the oxygen tent or chamber in oxygen therapy is mentioned, although complete directions with illustrations are given for administering the oxygen by nasal catheter.

However, the book contains a great amount of material with illustrations of charts, trays, and so on., that make it important for the reference library and for anyone to own who has need for information regarding nursing in a brief but accurate detail.

Very few textbooks are able to convey to the reader a sense of the spirit back of nursing that transforms simple tasks into a work of art. But it is just such features that bring a picture of a work that is full of life and spirit; "He can then be put to bed and should be given a hot drink and tucked up and made to feel happy, cheerful and contented as he looks forward to his future treatment."

Surely nurses everywhere should be proud of this book and although it may seem lengthy, it should be very profitable and enjoyable to anyone interested in actual bed-side nursing. M. S.

The Pathology of Diabetes Mellitus. By Shields Warren, M.D., Pathologist to the New England Deaconess, The New England Baptist, The Huntington Memorial, and the Pondville State Hospitals; Director of Massachusetts State Tumor Diagnosis Service; Assistant Professor of Pathology in the Harvard Medical School, Boston. With a Foreword by Elliott P. Joslin, M.D. Pp. 246; 86 illustrations and 3 colored plates. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $4.75.

The eight years that have elasped since the appearance of the first edition of this work have been rich in diabetic study, much of which affects

some phase of the subject considered here. The preservation of diabetic lives with improved use of insulin, and especially of protamine insulin, has emphasized such problems as the sclerosis of arteries (especially of the heart and legs), effects of insulin overdosage, surgical operations and so on. As in the first edition, pathologic physiology is properly emphasized, while the great amount of biopsy material, on which the pathologic anatomy is considerably based, reminds that here the living, as well as "mortui, vivos docent." The colored illustrations are excellent; this cannot be said of many of the black and whites. E. K.

DISEASES OF WOMEN. By Ten Teachers, under the Direction of CLIFFORD WHITE, M.D., B.S. (LOND.), F.R.C.P. (LOND.), F.R.C.S. (ENG.) F.C.O.G. Edited by SIR COMYNS BERKELEY, CLIFFORD WHITE and FRANK COOK. Pp. 492; 159 illustrations and 7 colored plates. Sixth Edition. Baltimore: William Wood & Co., 1938. Price, $6.00.

THIS manual on gynecology written by 10 English teachers of the subject, is a fine example of collective authorship. The subject matter presents the major headings concisely for the benefit of the student and yet there is sufficient emphasis on treatment to make the book particularly applicable to the practitioner. In the revision of this sixth edition, the sections on physiology and disorders of menstruation have been completely rewritten to bring it abreast of the present day ideas and advances. It is interesting that the chapter on radiology in earlier editions has been dropped. There has been added to those sections where radiation should be useful in treatments of the disease discussed a detailed description of the appropriate radiological methods. Without going into ethical or sociological indications for birth control the methods of contraception and of sterilization form the text of a new and well written chapter. There is a marked increase in the number of illustrations, particularly as regards histology.

This book may be regarded as an authoritative presentation of present day gynecological teaching and practice in England. P. W.

MEDICAL JURISPRUDENCE AND TOXICOLOGY. Edited by JOHN GLAISTER, M.D., D.Sc., Barrister-at-Law, Regius Professor of Forensic Medicine, University of Glasgow, etc. Pp. 747; 107 illustrations and 8 plates. Sixth Edition: Baltimore: William Wood & Co., 1938. Price, $8.00.

IN this edition less emphasis is placed on small-type interpolations. New material includes dermal and palmar prints, maggots, the Ruston Case, blood-grouping, seminal fluid grouping, war gases and so on.

E. K.

HUMAN POWERS AND THEIR RELATIONS. By K. W. MONSARRAT. Pp. 289; 60 figures. London: Hodder & Stoughton, Ltd., 1938. Price, 10/6.

THE material of this interesting book by an English biologist is obviously arranged with great care to make the sequence of ideas both clear and logical. After an orienting preface and a chapter of summary, placed at the beginning rather than the end of the book, the author proceeds to discuss the process of knowing and formation of ideas, then their relation to observed physical phenomena, biological phenomena from the simplest bacteria to the human being, and finally the conditions for equilibrium and freedom in man's social relations, with a comment on these relations in Britain at the present time. Any reproduction of the author's thesis in a review of this length must be extremely curtailed, but very briefly the propositions are these:

1. That knowing should be conceived as a process, definable only in terms of what it does: the production and presentation of reports, which may be itemized as ideas (p. 20).

2. That the self-derived idea "power-to-do" is given, primary and fundamental, it being the one idea irreducible to any terms but its own (p. 20).

3. That there is a duality in the relations of the process knowing. Those ideas (of the self) in which no "sensuous transactions" can be traced—*e. g.*, power, unity, enduring—are termed "identifications;" those ideas (of the whole world) in which sensuous transactions can be traced are termed "images" (p. 29).

4. That according to the proper use of ideas the world is to be conceived as occupied and wholly constituted by items of "power." The conception of items of "matter" is due to the duality of the knowing process, not to any duality belonging to the world itself (p. 20).

5. That much of the world is made up of groups of "power items," each group persisting through the mutual compensation without fusion of the power-items, and through the balancing contributions between the whole assembly and all the surrounding influences (p. 20).

6. That all action everywhere and at all times is interpretable as action toward an equilibrium (p. 21).

7. That the structure-integration of assemblies varies in complexity, different planes thereof being conceivable. The human being is to be conceived as an example of an influence-assembly, the human social group as an assembly in the making (p. 21).

8. That the ready maintenance of balance on one level involves the availability (freedom) of influence for the creation of balance-relation on a further level (p. 21).

9. That the conditions which govern the stability of assemblies in general, and their freedom for creating new relations, are discernible (p. 21).

The chief criticism which can be made of this thoughtful work is not so much of its content as of the implications and manner of its presentation. The author refers to his method of approach to these problems as "the historical method," apparently implying that it is original with him, and contrasts it with the "scientific" and "philosophical" methods, which he reproaches the one for "its peculiar interpretation of images as images of matter," and the other for "its abstraction and neglect of sensuous analysis and image-forming." Actually there is no essential difference between science's mechanical image, with its items of matter and their cause-effect relationships on the one hand, and the author's dynamic image, with its power-items and their "contribution" relationships on the other hand. Science does not concern itself with the corporeal nature of these items of matter, but with their individuality and relationships: according to Hobbes, a contemporary of Galileo, phenomena are, in their essence, motions, causes are the simple elements of motion, and effects are again motions. Also, it is far from true that philosophers have neglected sensuous analysis and image-forming; in the absolutely honest and consistent empiricism of David Hume, for example, there are many points of resemblance with the author's propositions, although Hume carries his idealism even further.

Enough has been given in the propositions outlined above to indicate that the author's detailed application of them to many biological and social phenomena are of absorbing interest to those having even a brief acquaintance with biology. In its construction and depth of thought this book is superior to many of the quasi-philosophical works of present-day physicists of otherwise good repute. A few of the propositions may be questioned; most of them are sound, although, as already stated, they are given in a misconception of the "scientific" and "philosophical" methods, and the insistence on a new set of names for what are really the same things is not neces-

sary. Fundamentally there is little that is new in the propositions. From statements made here and there in the book, including a penetrating one on the Heisenberg indeterminacy principle (physicists, please note) the author, while avoiding the terms mechanical and determined, apparently considers all world phenomena to be orderly and the order to be discernible, but the manner in which he unites the dual concepts of mind and matter into one of power-items is more reminiscent of the Leibnizian monad than anything else.

It is a pity that the author's apparent inadequate acquaintance with or inadequate comprehension of the history of philosophy should prove such a major defect in what is otherwise a work of deep, clear insight into problems which confront all scientists, whatever their field. R. S.

A Textbook of Histology. Functional Significance of Cells and Intercellular Substances. By E. V. Cowdry, Professor of Cytology in the School of Medicine, Washington University, St. Louis, Mo. Pp. 600; 323 illustrations, some in color. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $7.00.

Profiting by help of "true friends" who offered suggestions for improvement over the first edition, the author has added to this edition a valuable introduction (partly historical) and many illustrations (especially to show normal variations and the effect of ageing). He has not acceded to criticism that the book assumes too much preliminary training. "To cater to the least informed members of the class is not our purpose. When we expect but little of the students we receive little in return." The final bibliography, extensive for a book of this sort, carries out this thought. E. K.

Handbook of Practical Bacteriology. A Guide to Bacteriological Laboratory Work. By T. J. Mackie, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh; Honorary Bacteriologist to the Royal Infirmary, Edinburgh, etc., and J. E. McCartney, M.D., D.Sc., Director of Researches and Pathological Services, London County Council, etc. Pp. 586. Fifth Edition. Baltimore: William Wood & Co., 1938. Price, $4.00.

The main virtue of this book lies in its elementary straightforwardness and clear description of technical procedures. While there are other works on bacteriological technique that are of more value to the advanced worker, this one is a very helpful guide for the routine worker and those not having an extensive bacteriological background.

A serious effort has been made to bring this edition up-to-date, but it seems to have been only partially successful. A few pages may include all of the latest information on a given subject, only to relapse on other pages into sections which are several years behind the times. Several important recent innovations have been completely overlooked. Nevertheless, because of its simplicity and fundamental directness of approach, this book may well be regarded as one of the "primers" of the routine laboratory.

D. L.

The Harvey Lectures, Series XXXIII. Delivered under the Auspices of The Harvey Society of New York, 1937–1938. Under the Patronage of the New York Academy of Medicine. Pp. 275; 60 illustrations. Baltimore: The Williams & Wilkins Company, 1938. Price, $4.00.

This 33d volume of the well-known Harvey Lectures contains the following lectures: The Nature of the Visual Process (Selig Hecht); The Pasteur-Meyerhof Reaction in Muscle Metabolism (Einar Lundsgaard); The Func-

tional Significance of the Lymphatic System (Cecil K. Drinker); Transfers of Water and Solutes in the Body (John P. Peters); Studies on the Cortical Representation of Somatic Sensibility (Philip Bard); The Isolation and Properties of Tobacco Mosaic and Other Virus Proteins (Wendell M. Stanley); The Chemistry and Biology of Male Sex Hormones (F. C. Koch); Experimental Hypertension Induced by Renal Ischemia (Harry Goldblatt). The usual high standard of this Series has been maintained.

E. K.

THE CHEMISTRY OF THE STERIDS. By HARRY SOBOTKA, Chemist to the Mount Sinai Hospital, New York. Pp. 634. Baltimore: The Williams & Wilkins Company, 1938. Price, $8.50.

THIS is an excellent compilation of physical constants upon all the known derivatives of the sterols. Included in this class of chemical compounds are the bile acids, the antirachitic vitamins, the sex hormones, the cardiac glucosides, and some of the active substances of the adrenal cortex. The book will be of value largely to the chemical worker in the sterol field. Chapters upon the history of the subject, specialized methods of research, and upon the chemistry of bile acids are given as an introduction to the compendium upon physical constants. A complete bibliography is furnished at the end of the work, as well as a separate, convenient appendix of simplified structural formulas for 404 different sterol derivatives.

D. D.

SURGICAL PATHOLOGY. By WILLIAM BOYD, M.D., LL.D., M.R.C.P. (ED.), F.R.C.P. (LOND.), Dipl. Psych., F.R.S.C., Professor of Pathology, University of Toronto. Pp. 886; 476 illustrations and 15 colored plates. Fourth Edition, thoroughly revised. Philadelphia: W. B. Saunders Company, 1938. Price, $10.00.

IN this edition, which appears after an interim of 5 years, an introductory chapter which had been omitted from the third edition has been reinserted by request. "Among subjects which have been added to the present edition are the following: lymphogranuloma inguinale, primary thrombosis of the axillary vein, the grading of malignant tumors, glomus tumor (glomangioma) pilonidal cyst, uveo-parotid tuberculosis, Hashimoto's disease, parathyroid tumor, tuberculosis of the stomach, autolytic peritonitis, regional ileitis, ureterocele, the group of ovarian tumors comprising granulosa cell tumor, Brenner tumor and arrhenoblastoma, the pathology of the intervertebral disks, Gradenigo's syndrome, Clutton's joints, turban tumor of the scalp, and tumors of the islets of Langerhans. . . . New material has been included in relation to the experimental production of cancer, the etiology of tumors, heparin and thrombosis, mesenteric thrombosis, liposarcoma, implantation dermoids, carcinoma of the tongue, the relation of the hypothalamus to gastric ulcer, acute intestinal obstruction, the etiology of appendicitis, carbuncle of the kidney, the pathogenesis of renal calculi, endometrial hyperplasia, anaërobic streptococci in puerperal sepsis, the relation of chronic mastitis to carcinoma of the breast, and Ewing's tumor of bone." (Preface.)

E. K.

REFRACTION OF THE EYE. By ALFRED COWAN, M.D., Associate Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania; Attending Ophthalmologist, Philadelphia General Hospital, etc. Pp. 319; 172 illustrations and 3 colored plates. Philadelphia: Lea & Febiger, 1938. Price, $4.75.

THIS book on the refraction of the eye is unique in approaching the subject from the point of view of physiological optics. Most textbooks

on optics give no consideration to practical refraction, and the majority of ophthalmologists who write on practical refraction are not sufficiently conversant with geometric optics to deal with this most important fundamental basis of their subject.

Dr. Cowan has been teaching optics in the Graduate School of Medicine of the University of Pennsylvania for 19 years, and is widely known for his ability in correlating the theoretical and practical aspects of his subject. He has written a text which is badly needed and which will be found of value to all who are interested in the prescribing of glasses. F. A.

THE HISTORY OF BACTERIOLOGY. (University of London Heath Clark Lectures, 1936, delivered at The London School of Hygiene and Tropical Medicine). By WILLIAM BULLOCH, M.D., F. R. S., Emeritus Professor of Bacteriology in the University of London. Pp. 422; illustrated. New York: Oxford University Press, 1938. Price, $3.75.

THE bibliographical references to Bacteriology in the appendix of Garrison's History include only one independent work, Loeffler's *Vorlesungen* (1887), which was never completed. In 1930, Bulloch wrote an opening historical chapter in the Medical Research Council's *System of Bacteriology* which has stood for several years as the most satisfactory presentation of the subject. Having to give the Heath Clark lecture in 1936, Bulloch has now expanded his chapter of 103 pages into the present work. A large bibliography and alphabetically arranged biographical notices have been added and various sections expanded. The 11 chapter headings remained substantially as in the earlier effort. Carefully prepared by an authority on the subject, this book is valuable and reliable, though not perhaps as easy reading as the popular historical volumes now in vogue that seem not to hesitate to mix fact and fancy. E. K.

LIFE, HEAT AND ALTITUDE. Physiological Effects of Hot Climates and Great Heights. By DAVID BRUCE DILL, Fatigue Laboratory, Harvard University. Pp. 211; 25 illustrations. Cambridge: Harvard University Press, 1938. Price, $2.50.

THIS is a delightfully written essay, suitable both for the intelligent layman as well as for the physician and physiologist. Chemical and physiological data, secured from subjects exposed to the need for adjustment to the different conditions of life upon "the hot, low-lying deserts of the southwestern United States and the high, cold prairie or *puna* of South America" form the main topic of the work. Although it may appear to some that extreme adjustments to environmental conditions need be rarely necessary for the average organism, still the borderlands of physiology are extended by such studies. Practical value is also evident in such applications as aviation, mining, etc.

It is the opinion of the reviewer that the work is truly worthy of inclusion in the active library of all who are curious as to the possibilities and limitations of the human organism, under conditions of stress. D. D.

LIFE AND LETTERS OF FIELDING H. GARRISON. By SOLOMON R. KAGAN, M.D. With an Introduction by Professor JAMES J. WALSH. Pp. 287; 3 illustrations. Boston: The Medico-Historical Press, 1938. Price, $3.00.

WRITER of the world's most successful one-volume History of Medicine, eminent medical bibliographer and librarian, possessor of an arresting, vivid personality, Garrison well deserved, even was bound, to have his Life and Letters published. Yet one is surprised to find so soon a volume, which from the date on the Preface, appears to have been completed within 5 months of his death in April, 1935, though not published until 1938.

It contains notable material. The 7 chapters of Part I (77 pages) deal with his life and accomplishments under such headings as: "General Survey of Garrison's Life;" "Medical Historian and Medical Bibliographer;" "Medical Biography;" "The Teacher;" "Love of Music;" "The Man;" "Tributes." Wisely, most of the book is filled with his own letters, versatile, interesting, frequently pungent and intentionally provocative, and most revealing of the man. A bibliography and 4 appendices conclude the volume. Though containing a considerable number of typographical errors, the book has value. Its appearance sharpens anticipation of the volume that we understand is being prepared by Sigerist. E. K.

INJECTION TREATMENT OF VARICOSE VEINS AND HEMORRHOIDS. By H. O. MCPHEETERS, M.D., F.A.C.S., Formerly Director of Varicose Vein and Ulcer Clinic, Minneapolis General Hospital; Attending Physician, New Asbury, Fairview and Northwestern Hospitals, Minneapolis, and JAMES KERR ANDERSON, M.D., F.A.C.S., Instructor in Surgery, University of Minnesota School of Medicine; Fellow, American Proctologic Society, etc. Pp. 315; 82 illustrations. Philadelphia: F. A. Davis Company, 1938. Price, $4.50.

MCPHEETERS has rewritten his former book on the injection treatment of varicose veins and has been joined by Anderson, who has contributed a section on the injection treatment of hemorrhoids. The section on varicose veins written by McPheeters has been liberally revised, with enlarged chapters on anatomy and especially on embryology of the veins of the lower extremities. He has given good description of the involvement of the valves in the veins of the extremities. In the chapter on diagnosis he has gone into detail to point out the differential signs. The chapters on the Trendelenburg test and the pathology associated with varicose veins are similar to those in his previous book. One chapter is devoted to the question of operation in varicose veins. McPheeters, however, is more inclined to treat enlarged veins by injections. He believes that failure of injection treatment is due to imperfect technique. Ulcers of veins are treated by the author by the use of sponge pressure at the ulcer site and with the patient ambulatory. In large ulcers, after the tissues have become more healthy in appearance, he advises excision of the ulcer and applies skin grafts.

In the section on the injection treatment of hemorrhoids the usual outline is followed. The author recommends that hemorrhoids to be successfully injected must be internal, and should not protrude, or if at all only with defecation. Constant prolapsing of hemorrhoids is a contraindication to injection. He believes that only 25% of the internal hemorrhoids can be cured by injection alone, another 50% can be cured by injection and surgery. Those in which surgery is necessary are cases having an external varicosity which cannot be cured by injection. He believes that large prolapsing, fibrosed hemorrhoids or those associated with other anal lesions should be treated by operation. He describes the technique of injection and gives the various types of solutions which may be used. One is led to believe that the author feels the injection treatment of hemorrhoids is one not too sure of permanent result and not too free from complications.

L. F.

TRIUMPH OVER PAIN. By RENÉ FULÖP-MILLER. Translated by EDEN and CEDAR PAUL. Pp. 438; illustrated. Indianapolis: The Bobbs-Merrill Company, 1938. Price, $3.50.

WE cannot but regret the time spent in scanning this book. Instead of a well proportioned "story of mankind's age-old struggle with the problem of physical suffering, from beyond the dawn of history to that astonishing day when a little Boston dentist made the use of ether practical," we find a brief and unsatisfactory preliminary account of the battle with pain—

which up to the 19th century occupies 26 pages—while the overworked "ether controversy" occupies more than half the book (230 pages). Even this is not presented with historical accuracy. Whether in accordance with the Prefatory Note, "using his imagination the dramaturge conjures up the scene" recklessly, or whether from a desire to exalt Morton, at any rate the author fails to give Crawford Long the credit that history has definitely awarded him. It is *not* true that Long lacked confidence in his method, that he gave up the use of ether or that the news of his discovery did not spread beyond the confines of Jefferson. It *is* true that circumstances, certainly not discreditable to Long, prevented promulgation of his discovery; just as the statement on the Boston monument of the Good Samaritan is also true that ether anesthesia was "first proved to the world" by Morton in 1846.

The emotional, unreliable tone of the book is set in the Prefatory Note: "My book is the outcome of personal experience of pain, and is an attempt of the reason to unravel its mystery. . . . To liberate mankind from pain, heaven and hell were opened. . . . In virtue of his creative privilege, he (the dramaturge) breathes into the dead past until it regains a living soul." One would prefer a little less vivid drama, and a little more sober history, such as to include an account of the soporifics used so successfully in the Middle Ages, and a reasonable portrayal of the tremendous advances in anesthesia since Simpson's use of chloroform. But perhaps the versatile author, "who has written a number of books, including the popular 'Rasputin, the Holy Devil,' " was concerned with writing a good seller, and perhaps he was not overburdened with knowledge of his subject.

E. K.

Sulfanilamide Therapy of Bacterial Infections. With Special Reference to Diseases Caused by Hemolytic Streptococci, Pneumonococci, Meningococci and Gonococci. By Ralph R. Mellon, M.D., Dr. P.H., D.Sc. (Hon.), Director, Institute of Pathology, The Western Pennsylvania Hospital, Pittsburgh; Paul Gross, M.D., Pathologist to the Institute, and Frank B. Cooper, M.S., Research Chemist to the Institute. Pp. 398; 16 illustrations and 28 tables. Springfield, Ill.: Charles C Thomas, 1938. Price, $4.00.

The Authors' careful review of the literature and summary of the present knowledge of Sulfanilamide therapy should be extremely valuable to those unacquainted with the subject. The first section deals with the Chemistry and Pharmacology of the Sulfanilamide compounds together with their experimental and clinical employment; 200 different compounds are listed in the order of their relative activities. The second section reviews the experimental work done by the authors with particular emphasis on experimental pneumococcal infection. The third section is devoted to a study of the mechanism of action of sulfanilamide and the mobilization of the defensive factors in the host. The mode of action of these compounds continues to be a stumbling block. This presentation is especially good and although it does not completely clarify the issue, it seems to go a long way in the right direction. The experimental work dealing with the part played by the defensive factors of the host is most stimulating. The fourth section is devoted to general chemotherapeutic considerations with a discussion of the difficulty of evaluating therapeutic efficiency. The book closes with an addenda of work that has appeared after the manuscript had gone to press.

This book will be a valuable reference to the early work on Sulfanilamide therapy. As such its value stops there, as the volume of literature continues to increase from day to day. Already a dozen or more articles have appeared on the use of a new compound since publication that would appear to be better than any of the 200 listed. In the preface the authors seemed unduly

anxious to claim with two other workers in Baltimore the priority of introduction of the new drugs to this country. Cases, however, were treated in New York several months before any in Pittsburgh, and in Philadelphia at the same time as in Baltimore. D. P.

PATHOLOGICAL TECHNIQUE. A Practical Manual for Workers in Pathological Histology Including Directions for the Performance of Autopsies and for Microphotography. By FRANK BURR MALLORY, A.M., M.D., S.D., Consulting Pathologist to the Boston City Hospital, Boston, Mass. Pp. 434; 14 illustrations. Philadelphia: W. B. Saunders Company, 1938. Price, $4.50.

MANY years have elapsed since the appearance of the last edition of Mallory and Wright's Pathological Technique, and also since the death of the junior author. During that time technical methods have changed considerably and many valuable new ones have been added. "Clinical Laboratory Methods" and "Bacteriological Methods," subjects included in the older book, have also greatly changed and expanded, and a number of excellent books on these subjects are now available. It was undoubtedly, then, a wise step to omit them from the present work, which, though having the same title as the other volume, is put out as a first edition and in a changed format. Somewhat longer than the postmortem and histologic portions of the older book, and with a different order for the main subjects, the text is frequently reminiscent of the other work and old friends often appear among the illustrations. This is probably to be attributed more to the excellence of the earlier text than to failure to include modern improvements. Descriptions of older methods often remain quite unchanged, as indeed might well be the case from the reader's point of view. However, a gratifying number of new methods have been included, fulfilling the author's wish to present "a selection of those formulas that practical experience has shown to be of value," rather than "an encyclopedia of methods presented historically." The bracketted dates of announcement of many of the methods is a welcome addition, that one would have liked to have seen employed throughout. "Autopsy Methods," which now follows "Histological Methods" as Part III, has been made more useful by the addition of a section on autopsy permissions and inclusion of variants to the Virchow technique. A chapter on gross and microscopic photography is a good addition, though we regret that color photography was not also included. To older pathologists and technicians this volume will be welcome as a successful example of rejuvenation; for the younger generation it should soon make for itself a valued association. E. K.

THE FOOT. By NORMAN C. LAKE, M.D., M.S., D.Sc. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital, etc. Pp. 366; 353 illustrations. Second Edition. Baltimore: William Wood & Co., 1938. Price, $4.50.

THE second edition has improved its anatomical plates with colored illustrations. It has added two additional chapters. The one on "Congenital Club Foot" omits from its treatment the most effective conservative measures for resistant or recurrent deformity and advocates surgical procedures which should have been abandoned. The other chapter on "Foot Problems" should have included "traumatic osteoporosis," which again failed to be mentioned in the book. The chapter on "Flat Foot" has remained obscure in its presentation of treatment by manipulations, strappings, supports and exercises. This second edition detracts nothing from the value of the first. J. N.

ELECTROTHERAPY AND LIGHT THERAPY. By DR. RICHARD KOVÁCS, M.D., Clinical Professor and Director of Physical Therapy, New York Polyclinic Medical School and Hospital; Physician in Charge Physical Therapy, City Hospital, New York, etc. Pp. 744; 307 illustrations and 1 colored plate. Third Edition. Philadelphia: Lea & Febiger, 1938. Price, $7.50.

THIS book is the third edition in the short period of 5 years. The previous editions have been accepted as standard reference books on the subject of Physical Therapy; the appearance of this one shows the demand for such a work. In a rapidly growing subject, such as this, there are many changes in a period of 5 years. In this volume Dr. Kovács has brought Physical Therapy up to date with particular attention to the newer developments.

Short wave diathermy which has been of paramount interest in the past few years is thoroughly covered and a rational method of employing it has been elaborated. So many new machines are offered the physician that a clear exposition of short wave diathermy will be welcomed by the average physician.

The rest of the book describes various forms of treatment in which Physical Therapy is of value, laying stress on the physiologic effects. It enables the student to get a good general idea of the application of Physical Therapy as a whole.

This book is well arranged, covers the subject thoroughly, and in an up to date manner. A glossary of terms and a complete index increase its usefulness. It is well illustrated and should be in the hands of everyone interested in the subject of Physical Therapy. A reliable textbook in Physical Therapy has been badly needed and this book will be a valuable addition for the use of the student and the practitioner as well.

W. S.

LEHRBUCH DER PHARMAKOLOGIE, TOXIKOLOGIE UND ARZNEIVERORDNUNG. By DR. MED. EMIL STARKENSTEIN, O. ö. Professor of Pharmacology and Pharmacognosy in the German University in Prague. Pp. 758; 40 illustrations. Vienna: Franz Deuticke, 1938. Price, Paper, M. 20; Bound, M. 23.

THIS book is an attempt, by one of the senior pharmacologists of Europe, to emulate the well-known text of Meyer and Gottlieb in presenting the scientific basis of drug therapy by discussing the effects of drugs upon the various physiological systems of the body. As in its predecessor, a brief summary of the normal physiology opens each of these discussions, but here an attempt is made also to present some of the abnormal physiology involved in drug actions. Although the scope and plan of the book are extremely attractive, the Reviewer cautions the American reader that many of the statements concerning physiology and pharmacology are very different from those current in this country, and since there is no bibliography, and since authority for these statements usually is not indicated, the average reader will be unable to decide whether he is reading about authentic advances in knowledge or about opinions more or less peculiar to the author. Thus, while it may be true—as the author states—that strychnine and atropine do not stimulate anything directly but only remove inhibitions, that viewpoint is scarcely justified by existing evidence. Nor is it apparent to the Reviewer why the author should state categorically that tolerance to morphine probably depends largely upon deranged function of the suprarenal cortex. His opinion that methylene blue is useful in the treatment of carbon monoxide poisoning is no longer widely held in this country, and American readers will wonder at his statement that chewing tobacco con-

tains no nicotine. No mention is made of cyclopropane, nor of the use of barbiturates and ephedrine to reduce the hazards of local and spinal anesthesia, though these developments originated in this country a number of years ago. On the other hand, the sections on vitamines and hormones are well done and up to date. On the whole, the book may have limited value for the specialist in pharmacology but it certainly cannot be recommended to the American student and physician for the purpose for which it was intended; namely, to give the student or physician a comprehensive and trustworthy basis for bedside therapy. C. S.

NEW BOOKS.

The Medical Clinics of North America, Vol. 22, No. 5 (New York Number, September, 1938). Pp. 320; 45 illustrations. Philadelphia: W. B. Saunders Company, 1938.

Endocrine Therapy in General Practice. By ELMER L. SEVRINGHAUS, M.D., F.A.C.P., Professor of Medicine, University of Wisconsin, Madison, etc. Pp. 192; 39 illustrations. Chicago: The Year Book Publishers, Inc., 1938. Price, $2.75.

Behandlung Rheumatischer Erkrankungen mit Ultra-Kurzwellen. By PROF. DR. ERWIN SCHLIEPHAKE, Leitendem Arzt der Balserischen Stift. Band 8 of Der Rheumatismus, Sammlung von Einzeldarstellungen aus dem Gesamtgebiet der Rheumaerkrankungen. Herausgegeben von PROFESSOR DR. RUDOLF JÜRGENS, Berlin. Pp. 105; 27 illustrations. Leipzig: Theodor Steinkopff, 1938. Price, Rm. 7.00.

Drastische Hautreizbehandlung. Heilwege bei Inneren Erkrankungen. By DR. WALTER RUHMANN, Specialarzt für Innere Krankheiten in Berlin. Pp. 115; 20 illustrations. Leipzig: Krüger & Co., 1938. Price, Paper, M. 3.80; Bound, M. 4.80.

Der Zyklus der Frau. Reform des Ehelebens. By DR. JULES SAMUELS, Chirurg-Frauenarzt, Leiter der Einrichtung für Kurzwellentherapie, Amsterdam. Pp. 175; 43 illustrations (some in colors). Hague: G. Naeff, 1938. Price not given.

Dental Science and Dental Art. Edited by SAMUEL M. GORDON, PH.D., National Research Council Fellow (Biological Sciences) 1926–1928; Director, American Dental Association Bureau of Chemistry, and Secretary of the Council on Dental Therapeutics, American Dental Association, 1928–1937. Nineteen Contributors. Pp. 731; 224 illustrations and 61 tables. Philadelphia: Lea & Febiger, 1938. Price, $9.50.

Modern Anaesthetic Practice. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 231; illustrated. London: Eyre & Spottiswoode (Publishers), Ltd., 1938. Price, 10s. 6d.

Insulin. Its Chemistry and Physiology. By HANS F. JENSEN, PH.D., Associate, Laboratory for Endocrine Research, The Johns Hopkins University. Pp. 252. New York: The Commonwealth Fund, 1938, Price, $2.00.

Bulletin of the Health Organisation of the League of Nations, Vol. 7, Nos. 1, 2 and 3. (February, April and June, 1938.) Pp., No. 1, 1–167; No. 2, 168–427; No. 3, 427–607; all illustrated. New York: Columbia University Press, 1938. Price, 65c each; annual subscription (6 numbers), $3.75.

Jacob Henle: On Miasmata and Contagia. Translated by GEORGE ROSEN, M.D. Pp. 77; 1 illustration. Baltimore: The Johns Hopkins Press, 1938. Price, $1.00.

Biology and Pathology of the Tooth and Its Supporting Mechanism. By BERNHARD GOTTLIEB, Research Professor, Columbia University Dental School, etc., and BALINT ORBAN, Assistant Professor, Northwestern University Dental School, Chicago, etc. Translated and Edited by MOSES DIAMOND, Associate Professor, Columbia University Dental School, New York; Head of Dental Anatomy Department. Pp. 195; 166 illustrations. New York: The Macmillan Company, 1938. Price, $5.00.

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NEW EDITIONS.

Human Pathology. A Textbook. By HOWARD G. KARSNER, M.D., Professor of Pathology, Western Reserve University, Cleveland, Ohio. With an Introduction by SIMON FLEXNER, M.D. Pp. 1013; 461 illustrations (18 in color). Fifth Edition, revised. Philadelphia: J. B. Lippincott Company, 1938. Price, $10.00.

The Practice of Medicine. By JONATHAN CAMPBELL MEAKINS, M.D., LL.D., Professor of Medicine and Director of the Department of Medicine, McGill University; Physician-in-Chief, Royal Victoria Hospital, Montreal, etc. Pp. 1413; 521 illustrations (43 in color). Second edition. St. Louis: The C. V. Mosby Company, 1938. Price, $12.30.

Appendicitis, omitted from the first edition as a surgical condition, has been included in this edition. "Among the conditions which have been amplified or added are the following: acute laryngotracheobronchitis; tuberculous tracheitis; 'cysts' of the lung; Friedländer pneumonia; lipoid pneumonia; monocytic leucemia; nutritional edema; protamine zinc insulin; experimental nephritis; vascular renal failure; congenital aplasia of the kidney; uremic state; sulphanilamide therapy; lymphogranulomatosis inguinalis; epidemic pleurodynia, and cannabis indica intoxication." The numerous illustrations—an unusual and valuable feature of a textbook on the Practice of Medicine—have been revised and amplified. E.K.

Interns Handbook. A Guide, Especially in Emergencies, for the Intern and the Physician in General Practice. By Members of the Faculty of the College of Medicine, Syracuse University. Under the Direction of M. S. DOOLEY, A.B., M.D., Chairman, Publication Committee. Pp. 523. Second Edition, revised and reset. Philadelphia: J. B. Lippincott Company, 1938. Price, $3.00.

Intern and practitioner will here find a wealth of practical information, much of it of a type useful in emergencies and gathered by many collaborators not only from textbooks but also from medical journals, all of it encompassed in a handy little pocket-size volume. It is highly recommended. R.K.

The Principles and Practice of Perimetry. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., F.A.C.S., Professor of Ophthalmology in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Graduate Hospital of the University of Pennsylvania, etc. Pp. 331; 222 illustrations and 5 colored plates. Fourth Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1938. Price, $4.50.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY.

UNDER THE CHARGE OF

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RECENT ADVANCES IN PLASTIC AND RECONSTRUCTIVE SURGERY OF THE EAR, NOSE AND THROAT.

THE demands for reparative and reconstructive procedures about the head and neck are becoming more frequent. This is due in no small measure to the increasingly large number of deformities subsequent to industrial hazards and automobile accidents. A further factor is the slow but definite change in attitude towards plastic surgery from the earlier view that it was only the sphere of the plastic quack or pseudosurgeon. It is acknowledged today that there is a definite indication for these procedures, not only from the esthetic point of view but also as a means of economic rehabilitation, as well as a measure to prevent or treat the ever-present phobia or psychoneurosis. It is highly suggestive of the trend of the times to note that departments of plastic surgery are being brought into existence in hospital after hospital. This tendency is in support of the contention of Davis[16a] that a special branch of surgery has come into existence. In this same contribution he outlines the type of organization that he considers should be adopted by large institutions in order that such service may be available in every community. The possibilities of scientific and honest plastic surgery providing it is practiced by skillful, honorable and qualified surgeons is discussed by Beck,[6] who comments on the aims and future of this specialty and traces its development. The medico-legal aspects of plastic surgery, which may be of much practical importance, has received scant attention in the literature. Maliniac[37a] contributes a lengthy and minute exposition of the subject. He decries the indolence of the legal and medical profession in protecting the public against the unqualified and quack practitioners, and believes that greater aid should be extended to qualified and well-trained surgeons who employ recognized methods in relieving functional and anatomic abnormality. He feels that the possibilities of expert repair

should be taken into account in consideration of the amount of indemnity for deformities arising from industrial and other causes. More information along these lines should be available to hospital staffs and executives that are hesitant in recognizing or creating such departments. The recent announcement of the formation of the American Board of Plastic Surgery is further confirmation of the definite existence of this specialty. The functioning of this examining board will assure the public of properly qualified surgeons. Plastic surgery is an intimate part of ophthalmology, otolaryngology, maxillofacial and oral, and dental, as well as general surgery. Blair[8a] believes that the basic training should be a thorough grounding in general surgery. Hays[28] advocates that the otolaryngologist perform the plastic procedures in the repair of tracheotomy wounds, pharyngeal adhesions, septal perforations, auditory canal atresias, postauricular fistulæ and outstanding ears.

In consideration of indications for plastic and reconstructive procedures, gross deformity or abnormality has been accepted by the profession with little if any question. On the other hand, minor defects and slight deviations from the normal, as a rule, have been denied correction by orthodox practitioners in the past. The mental anguish that many individuals with but slight defects experience, not infrequently may lead to a definite psychoneurosis or real psychosis. Blair[8b] discusses in a masterful way the psychic reactions and the attendant handicaps of such individuals. In a group of illustrative cases of various types of facial defects associated with various manifestations of mental trauma, he definitely assumes the attitude that the indications for surgical repair require a consideration of the psychic reaction as well as the featural deformity. Gillies and Mowlem[23] also insist that early treatment of physical defects definitely reduce the incidence of secondary psychologic trauma to a minimum. Straith,[59a] in an extensive dissertation on the psychologic aspects of plastic surgery, discusses at great length the psychic distress and feeling of inferiority, that many individuals exhibit with featural defects. Using a large series of cases he describes the success that has attended such procedures in socially, mentally and economically rehabilitating these unfortunates. It is generally conceded that an abnormality that is sufficient to impair function or interfere with social intercourse or economic endeavor, not only is admissible but is actually desirable of repair. However, we have had difficulty when presented with a slight disfigurement that is not objectively conspicuous. It is admitted that all individuals vary in their mental reactions. We have repeatedly observed patients with monstrous defects that are actually repellent to the observer in whom little if any psychologic disturbance is evident. On the other hand, we have more frequently observed an unusual psychic disturbance markedly out of proportion to a minor or infinitesimal defect. Our experience with such individuals is a most unhappy one. More often than not, the procedure has not influenced the mental condition unless, to exaggerate it. Maliniac[37b] has had similar experiences, and advises a careful psychologic appraisal of the patient with a defect out of all proportion to the mental state that is exhibited. Such psychic instability should be an absolute contraindication for the procedure, as the surgery may supply a new focus for the obsession.

Not infrequently such an obsession may appear after the operation and the subsequent course may be trying to the surgeon and patient alike, who exhibited no such mental abnormality before operation. In consequence, we are reluctant to accept individuals with but minor defects unless there is a good motive underlying the request. It might be well when in doubt to seek psychiatric consultation and avoid subsequent regret.

Nasal Plastics. Plastic surgery of the nose is, in all probability, the most common procedure within this field that the otolaryngologist is called upon to perform. The operations for removal of an unsightly hump or the correction of a depressed dorsum have been fairly well standardized. In the case of the depressed dorsum or saddle nose, the usual procedure is to effect a subcutaneous elevation of the soft tissues above the bony dorsum and insert some rigid material for support. In addition to bone and cartilage, foreign bodies such as celluloid and ivory have been utilized. Notwithstanding the known temporary tolerance that tissues have for foreign bodies, reports of their continued use appear. Mortnick[40] advocates the use of ivory, and Golden[24] advocates the use of celluloid as well. Maliniac, who originally introduced the use of ivory into this country, no longer employs the material. In our own hands, the number of expulsions were so great that we discontinued their use some 10 years ago. A real innovation is the use of preserved isografts of cartilage, that is reported by Spanier[58] and by Straith and De Kleine.[60] Cartilage obtained from another person is preserved in an aqueous solution of merthiolate and kept in a refrigerator. They report that the percentage of takes with this material compares favorably with fresh autogenous cartilage removed from the patient. This may be the answer to the situation when an individual refuses to supply a supporting substance from some other part of his body. Cartilage continues to give better end results than bone. We have noted that bone has a tendency to atrophy and become absorbed, in spite of repeated assertions that bone implants will live if placed in contact with bone. McIndoe,[34a] in treating on the restoration of nasal depressions with cartilage grafts, notes that although cartilage will live when placed within living tissue, bone may disintegrate and he calls attention to the fact that the use of bone only is attempted by those that do not keep pace with the literature. He gives the results of experiments with cartilage grafts in various forms utilized in depressions of different degrees. Depressions and deformities of the nasal tip are treated in great detail by Straith.[59b] The nature and extent of the deformity determine the procedure he employs. Small defects in the skin are covered by Wolfe grafts obtained from the upper eyelid or back of the ear. Defects of the ala are corrected by small flaps from the nose or nasolabial folds. Extensive losses of tissue require delayed flaps from other parts. Slight cartilaginous depressions just above the tip are repaired by the introduction, subcutaneously, of small pieces of auricular cartilage. Broad depressions necessitate the use of rib cartilage or Straith's modification of Kazanjian's procedure, in which he everts the cut ends of the upper lateral cartilages and sutures them back to back in the midline to provide support. A simple method of reducing an abnormally protruding nasal tip is described by Wahl.[63]

A method of correcting a lateral deviation of the nasal tip by means of excision of the large asymmetric triangular cartilage is described by Tamarin.[61] A most detailed and complete presentation of the repair of nasal deformity due to loss of tissues from various causes is presented by Pierce and O'Connor.[50] In this article they stress the use of pedicled grafts obtained from neighboring parts.

Plastic procedures about the nasal tip are not restricted to anatomic deformities. Not infrequently impaired nasal respiration may be due to a congenital weakness of the nasal ala causing them to be drawn in during inspiration. Upon elevating the tip of the nose, so as to prevent the tissues from being inspired, the obstruction to breathing may be eliminated. Rethi[52] describes a method of stiffening the ala, by removing a piece of the lateral crus of the alar cartilage, so as to effect a nonyielding scar, or by excising a sickle-shaped piece of skin that raises the alar cartilage away from the septum. Organic stenosis of the anterior nares is treated by O'Connor[44a] by excising the stenotic tissues and replacing them by a Thiersch graft. Nasal obstruction due to a lateral displacement of the lower part of the septum into one nostril or the other may be a cause of poor respiration as well as disfigurement. Operative procedures for repair of this condition are described by Metzenbaum,[39] Cohen,[13] and Peer.[48] Congenital bony atresia of the posterior nares with operative cure is described by Kearney,[32] Colver,[14] Anderson,[1] Donnelly,[18] and Childrey.[12] The tendency for the opening to undergo cicatricial stenosis was overcome by Donnelly[18] in the use of a whole skin graft.

The management of nasal fractures constitutes one of the most important phases of rhinoplasty. As far as our personal experience is concerned, the primary treatment of such fractures apparently receives but cursory attention at the hands of the profession. While some attempt is made towards repositing the fragments to secure as little external deformity as possible, most individuals make little if any effort to investigate the internal architecture of the fractured nose to determine whether or not a patent airway is present and maintained. The increasing number of nasal and facial fractures as a result of the automobile, industrial and sport hazard should impress us with the necessity of observing that due precaution is taken in the treatment of these accidents in order to prevent the hazardous sequelæ of nasal deformity and impaired nasal respiration. Most fractures are amenable to reduction and immobilization. As Safian and Tamerin[55] state, the nose is composed of several individual structures, and unless a detailed analysis of the structures involved is made, the treatment may be incomplete. Straith and De Kleine[60] insist on careful reposition of the fragments and stabilization by adequate splinting devices. Salinger[56] advocates the use of soft metal splints, while New[42] uses a mattress suture passed through the nose and secured with lead buttons in some cases. Watkins[66a] also emphasizes early replacement and immobilization of the fragments. Watkins[66b] uses a hairpin-shaped splint. If there is loss of overlying soft tissue Straith[59b] believes that it should immediately be replaced with a Wolfe graft. Kazanjian,[31a] in a discussion of nasal injuries, insists that great care must be taken in selection of these grafts from the point of view of texture and coloration as well as visibility. The repair of old unreduced fractures is

treated by McIndoe,[34b] Fomon,[21] Straith and De Kleine,[60] and Safian and Tamerin,[55] who find that various procedures may be required to repair such uncalled for end results as dislocated septi, dorsal depressions, deviations from the midline, as well as humps and exostoses produced by callous formation. Facial deformity is most commonly due to accidental trauma or disease. At times surgical procedures for carcinoma about the face leave marked postoperative defects. The repair of large defects of the cheek following radical resection for malignantly diseased upper jaws is described by Beck and Guttman,[7] Prudente,[61] New and Figi,[43] and Figi[20] by the use of various types of sliding and travelling flaps. A sufficient interval of time should elapse before contemplating the reconstruction in order to assure ones' self that a recurrence of the growth is not likely to be manifested. In the interval, which should be one or more years, an artificial prosthesis may be worn. Olinger and Axt[45] and Kazanjian[31c] describe such prosthetic devices in oral and facial defects, and indicate their use when surgical repair is impossible for various reasons. The source of the graft in repairing facial defects is treated by Maliniac,[37c] who advises a rotating or sliding graft from the immediate area of the defect. Here the color and texture of the skin closely approximates that of the area lost. If this is not feasible then tube grafts from the forehead, back of the ear or from the neck is advised. The early care of face injuries is discussed by Blair, Brown and Byars.[10] They advise immediate suture of all cuts into the ear, border of lip and eyelid, or the nasal skin and underlying cartilage. A most interesting account of the successful healing of a nasal ala that was completely torn away from the nose is reported by Roy.[54] He sutured the ala to the nose some 3 hours after the accident had occurred. Davis[16b] describes the use of the vertical mattress suture, and Straith[60c] describes the use on subcuticular suture in dealing with facial scars.

Nasopharynx. As a result of a poorly performed tonsil and adenoid operation, extensive destruction following a severe Vincent's infection, or infrequently today in comparison with the past, of lues, one may be confronted with a stenosis of the nasopharynx. Pharyngeal reconstruction for such a condition is described by O'Connor,[44b] who utilizes a Thiersch graft placed into the opening created by the removal of the scarred tissue to prevent its recurrence and subsequent stenosis. There are a number of contributions by Riemke,[53] Vaughan,[62] Blair and Brown,[9] Ivy,[30] Wardill,[64] and Brown[11] on various aspects of cleft palate surgery. A method of utilizing an intratracheal device for anesthesia is described by Ayre[3] for use in infants. The mechanism of the soft palate and surrounding structures in the production of speech was studied by Wardill and Whillis[65] in a patient in whom an operative defect permitted direct vision, while Parsons[47] reviews the various factors that interfere with the production of normal speech in cases of cleft palate. It was assumed in the past that the characteristic speech, when once developed, persisted after the closure of the palate. However, this type of rhinolalia is due to an inadequate length of the reconstructed palate that does not permit of efficient closure of the nasopharynx. Vaughan[62] describes a new incision that allows for greater lengthening of the resulting palate that may prevent the occurrence of the speech defect, while Wardill[64] employs a pharyngo-

plasty to aid in narrowing the nasopharynx. That the repair of the cleft palate is not always accompanied by a successful result at the first attempt is indicated by Padgett,[46] who reports on 184 cases in which the primary operation was unsuccessful to some degree or other. He describes several procedures in such cases varying with the amount of tissue lost. He finds that these cases had an average of 2.3% unsuccessful operations per patient.

The abnormally protruding or receding chin also has been subjected to active interference. In the past, operative procedures for increasing the prominence of the chin consisted in the main of the introduction of ivory or preferably costal cartilage subcutaneously. Kazanjian[31d] and Babcock[4] describe operations upon the mandible and on displacement of the condyle respectively to aid in accomplishing the same purpose. The mandible is also partially resected and reposited by Kazanjian,[31d] Hensel,[29] and Pettit[49] in reconstructing the protruding jaw of prognathism.

The closure of laryngostomic fistulæ and enlargement of the tracheal lumen by means of excision of the cicatrix and the use of a pedicle flap and cartilage is described by Babcock[4b] and Looper.[33]

Plastic surgery of the ear in the past has concerned itself mainly with protruding ears and the closure of postauricular fistulæ. While postauricular fistulæ are relatively uncommon today, a few cases may be seen at rare intervals. The most common cause has been the practice of continuous packing of the mastoid wound until an ingrowth of the dermal epithelium met an outgrowth of the mucosal epithelium of the mastoid antrum. As an aid in the prevention of their occurrence, McNichols[35] has described an incision in which the posterior flap is split into two layers that are individually sutured. The same principle is utilized by Ashley[2] and Copps and McCormick[15] in closing a postauricular fistula, in which he obliterates the mastoid cavity with the inner layer and closes the external defect by the outer layer. Protruding ears can be easily corrected by removing elliptical sections of the auricular cartilage and skin. In the past, the failure to realize a successful result was due to the practice of excising the skin only and suturing the auricle in closer approximation to the head without touching the cartilage. As the elastic auricular cartilage acted as a spring, the constant tension caused the skin to stretch and after a period of time, the ears protruded once more. Davis and Kitlowski[17] report on a new method involving excision of the cartilage that gave excellent results. They feel that the best age for operation is from 4 to 5 years and claim that there is no interference with the subsequent development of the ear. Graham[26] and MacCollum[36] also describe technique based upon the principle of excision of the cartilage. The surgical attack upon the cartilage brings the possibility of a deforming chondritis into mind. Such a complication can be avoided by strict attention to asepsis and the obliteration of all dead space and crevices in the postoperative dressing. Goodyear[25] discusses measures to prevent such a complication. While there has been a great deal of energy expended in attempting to construct an entire ear in cases of congenital absence or rudimentary ears, they have for the most part been absolute failures. Most of the end results were merely the substitution of monstrosity for deformity. However, Gillies[22] and Nattinger[41] have reported on

a method of utilizing maternal ear cartilage as a means of support that may offer encouragement in obtaining more pleasing esthetic results. Facial paralysis presents a most arresting deformity. In the past, the use of hypoglossal and spinal accessory nerve anastomosis left a good deal to be desired. Such anastomosis resulted in facial spasms when using the tongue or arm. In addition, facial changes corresponding to emotional changes would only occur on the unaffected side, so that one laughed or showed anger or sorrow with but one side of the face. Sheehan[57] and Halle[27] advocate the use of temporal and masseter muscle slips in association with strips of fascia attached to the angle of the mouth. The most revolutionary tendencies have been in the direction of suture of the facial nerve. A successful direct suture of a divided nerve is reported by Martin[38] with the principle of removing the nerve from its bed so as to give the few additional millimeters of length necessary for the approximation of the severed ends. When this is not feasible the procedure of bridging across the defect with a nerve graft from the superficial femoral nerves is described by Ballance and Duel.[5] The results with this technique so far surpass the use of the method of nerve anastomosis as to relegate the technique into the limbo of medical history. While most cases of Bell's or refrigerant palsy get well, some remain more or less permanent. The condition is due to an edema of the nerve within its non-yielding bony canal with resultant pressure atrophy. Duel and Tickle[19] found that 80% of these cases did not entirely lose their reaction to the faradic current and finally recovered. The remaining 20% lost their faradic response in 2 or 3 days and were permanently paralyzed. The total loss of the faradic response should be the indication for immediate decompression of the nerve in the canal by removal of the overlying bone.

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NEUROLOGY AND PSYCHIATRY.

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ELECTROENCEPHALOGRAPHY.

BERGER[4] was not the first to demonstrate potential changes arising from the brain, but it was largely his work, coming at a time when advances in the knowledge of electricity had provided suitable apparatus, that stimulated the great mass of research on this phenomenon. That a great deal of work is being done is attested to by the fact that, in the Quarterly Cumulative Index Medicus for the first 6 months of 1938, 37 of the 77 titles listed under Physiology of the Brain deal with some aspect of the electrical activity of the cortex.

Although electroencephalography has been frequently likened to electrocardiography, the analogy is hardly a close one, since the electrocardiogram records action potentials, while at least some of the potentials of the electroencephalogram are ascribable to lack of activity of the units involved. The apparatus is, however, essentially the same,

consisting of electrodes for application over the area to be investigated, an amplifier employing vacuum tubes, and a recording device. Greater amplification is required than with electrocardiography, as the potentials to be recorded are approximately one-tenth as great, varying from 5 to 100 millionths of a volt, when taken by electrodes placed on the scalp. From the exposed cortex, they may be 50 to 100 times this large. The apparatus used by various workers lacks uniformity, both in the frequency characteristics of the amplifiers and of the recording units. When to this is coupled a lack of standard types of electrodes and derivations of the leads, it is not remarkable that some discrepancies between the records obtained by different investigators have resulted.

In general, two types of waves are recognized to occur in the normal subject. The alpha waves, sometimes spoken of as the "Berger rhythm," are characteristically found when the electrodes are placed over the occipital region of a mentally tranquil subject who has his eyes closed. They are of a frequency from 8 to 12 per second, and roughly sinusoidal. They disappear in most subjects on opening the eyes in the light, and in all when reading. Emotional tension also causes them to disappear. They are quite characteristic for form and frequency for each individual,[27a,b] while in some normal people they do not occur at all. Their rate may be increased up to about 18 per second by exposing the eyes to a flickering light source of similar frequency.[1] It is felt that they are probably representative of the synchronous resting discharge of the neurones of the occipital cortex.[3]

The beta waves are of lower amplitude and higher frequency, from about 18 to 30 per second. They may be found anywhere over the cortex, but are particularly prominent over the motor area.[10] Some doubt has been cast on their relationship to cerebral activity, and they have so far proven of little importance.

Besides these normal waves, there are waves, to be described later, associated with epileptic seizures, and slow, large amplitude waves of 1 to 6 per second, called delta waves, associated with dysfunction or disintegration of the cortex.

Factors Influencing Normal Rhythms. It has been shown that alpha waves do not appear before the age of about 4 months, and that at this time they are rare, and of a frequency of about 4 per second. This frequency increases with age, until at 8 years they attain the adult average, which is 10.2 per second in men and 11.0 in women.[23] This correlates well with the findings in mental defectives, where the alpha rhythm is slower than normal for mental ages below 5 years, and normal above that mental age.[20]

The state of consciousness has a marked effect on the alpha rhythm. Five levels of consciousness associated with falling asleep may be delineated.[11] With the subject wide awake, the normal alpha rhythm of 10 per second is present. As drowsiness comes on, the amplitude of the alpha waves diminishes, and they are present less of the time. Then short groups, or "spindles," of waves of 14 per second appear, with occasional low frequency delta waves, which are not present in the normal waking encephalogram. The 14 per second waves then become greater in amplitude, and delta waves become more frequent, until finally in deep sleep there are many large delta waves and spindles of 14 per second waves. Thus it is essential in passing on the normality

of an electroencephalogram to know the state of consciousness of the subject. Hypnosis does not produce the changes characteristic of sleep, but hypnotic suggestion of light will abolish the alpha waves of a subject with eyes shut.[5,25] Unconsciousness from other causes, as in syncope and in coma from increased intracranial pressure, produces essentially the same changes as does sleep.

Breathing pure oxygen produces no change in the alpha waves,[8] but asphyxia, as in breathing nitrogen, induces changes characteristic of sleep. Inhalation of 20% carbon dioxide increases the frequency and decreases the amplitude of the waves, while hyperventilation causes no change until, in the period of apnea, oxygen lack calls forth the same changes as are seen in asphyxia.

A significant relationship has been shown between basal metabolic rate and alpha rhythm, the latter being increased in rate in subjects with a high metabolic rate, whether due to thyroid disease or induced by thyroxin injection. No significant relationship with pulse, blood pressure, or body temperature could be demonstrated.[24] The shift in rate during the advancing progress of cortical involvement in paresis probably reflects shifts in the cellular respiration rate of the cortical cells.[17]

Those drugs which alter the state of consciousness are particularly effective in changing the alpha rhythm. Bremer[7a] has shown that ether and chloroform produce a slowing of the rhythm, which he believes is due to a marked depressant action on the cortical cells. Barbiturates, on the other hand, increase the amplitude of the already present alpha rhythm, an effect similar to that seen in animal preparations in which the cortex is separated from its lower centers surgically.[7b] He believes that this is due in both cases to an effective de-afferentation of the cortex, allowing the cells to beat synchronously at their resting rate, without interference from incoming stimuli.

These results were in part confirmed by Derbyshire *et al.*,[12] who found increased amplitude of alpha waves with light barbiturate anesthesia, but disappearance of waves as the anesthesia deepened. They found waves of 30 to 40 per second in ether anesthesia, sometimes superimposed on large, slow waves. Lennox, Gibbs, and Gibbs[22] found barbiturates and bromides to decrease frequency and increase amplitude of waves. The increased amplitude of waves in anesthesia is ascribed by Adrian and Matthews[2] to the cutting off of afferent impulses which if allowed to reach the cortex would diminish synchronous activity. This is in accord with Bremer's hypothesis.

Mescaline, especially when producing visual hallucinations, tends to suppress the alpha rhythm.[26] Small doses of acetylcholine and of potassium by the intracarotid route in animals in which the cortex has been "isolated" increase the frequency of waves, while large doses diminish activity. Calcium in all doses diminishes activity, bearing out the calcium-potassium antagonism.[6] Strychnine applied locally to the cortex in very dilute solution augments electrical activity, while higher concentrations cause sharp, rapid potentials, due to rhythmic spontaneous discharge of groups of pyramidal cells.[7c] Alcohol in large doses produces the large, slow waves characteristic of unconsciousness. Scopolamine and morphine first decrease the amplitude of the waves, and later may cause bursts of large waves at a 10 per second rate.

Drugs acting on the autonomic system have not been shown to produce any changes.[14a]

In Pathologic Conditions of the Nervous System. Lemere[21b] has shown that in normal individuals the alpha waves are of the same amplitude on the two sides of the head, while in patients with unilateral lesions of the frontal lobe, notably abscess and tumor, the waves on the affected side are of greater amplitude. In lesions of the parieto-temporal regions which destroy the optic radiations, the alpha rhythm remained present on the affected side even with the eyes open, while it disappeared on the unaffected side when the eyes were opened. In widespread lesions destroying the occipital lobe, the alpha rhythm was absent. Jacksonian epilepsy gave rise to large potentials of spike form, while the visual aura of migraine suppressed the alpha rhythm, which later returned while the headache persisted. In organic dementia the alpha rhythm was poorly manifest.

Walter[29a,b] has demonstrated that abnormally large, slow waves, designated delta waves, are regularly present over areas of cortical dysfunction or disintegration. He has been notably successful in localizing cerebral neoplasms by this means. He utilizes three separate amplifier systems, and by disposing his electrodes over one side of the skull after the manner employed by Adrian, is able to determine the site of origin of the abnormal potentials by observation of their phase relations in the various leads. In 38 cases of suspected tumor, 12 showed delta waves from a single focus, which on operation proved to overlie a tumor. Of the 26 cases showing no abnormality, 23 were ultimately proven to be free from tumor, and of the remaining 3, 2 had cerebellar tumors and 1 an eighth nerve tumor. He called attention to the diffuse presence of delta waves in states of increased intracranial pressure, which must first be reduced before localization is possible. Case[9] was able to localize a tumor by this means.

Lennox and his co-workers[13,14b,15] have found abnormal potentials with the occurrence of epileptic attacks. Grand mal attacks are characterized by rapid, spike-like waves, psychomotor attacks by slow waves, and petit mal attacks by a combination of slow round waves and sharp spikes. The characteristic petit mal waves may be seen when the patient is not aware of having an attack. Attacks may be predicted beforehand by the appearance of the characteristic wave pattern, while the effect of therapy may be judged by the action of drugs on the abnormal potentials. Lennox has called epilepsy a "paroxysmal cerebral dysrhythmia," and has stated[14b] "a clinically observed seizure is but the outward manifestation of a disordered rhythm of brain potentials."

Golla, Graham, and Walter[16] have found pathologic delta waves in about half of some 200 epileptics examined by them. Those patients suffering from grand mal attacks of idiopathic nature almost invariably showed a focus of delta waves on one or both sides of the head. Delta waves were more conspicuous in young than in old epileptics. They found no difference in incidence of delta waves in patients under treatment with barbiturates and bromides and in those not under treatment. On the hypothesis that the presence of delta waves indicated a depression of cortical function, one patient was given a cortical stimulant, benzedrine sulphate, with disappearance of both delta waves and attacks, both of which returned on discontinuing the drug.

Hoagland *et al.*,[18] found that patients with schizophrenia showed an increased incidence of delta waves. He demonstrated that, after a large dose of insulin, the incidence of delta waves bore an inverse relationship to the level of blood sugar, and that some schizophrenics after insulin therapy showed a decrease in the number of delta waves coincidental with clinical improvement.

Travis and Malamud[28] found no difference between the electroencephalograms of normal and schizophrenic subjects. They observed that stutterers showed showers of sharp spikes coincidental with their inability to speak. The appearance of these potentials is such, however, as to raise the suspicion that they may be muscle action potentials incidental to the grimacing not uncommon in stutterers under these circumstances.

Schizophrenics have been shown to have a relatively "poor" alpha rhythm, while manic depressives have "good" ones, and this tendency is carried over to non-psychotic individuals of these personality types.[21a] Hughes, Strecker, and Appel[19] have found waves of a frequency up to 500 per second in schizophrenia, as well as in the apneic phase after overbreathing. These are so far beyond the frequencies previously reported as to make their significance difficult to evaluate.

In mental deficiency, the frequency of the alpha waves seems to parallel mental rather than chronological age, the rate being essentially normal in those mental defectives with a mental age over 5 years.[20]

Thus it is seen that a great mass of factual data has been secured by the use of the electroencephalograph. The method has been applied to many unrelated pathologic conditions, and it is not surprising that with widely varying apparatus some conflicting results have been obtained. Sweeping conclusions are not justified in the light of the fragmentary data now at hand, yet it is already clear that the electroencephalograph is a valuable tool in the study of nervous function. Whether the potentials recorded are a direct reflection of the activity of the neurones, or are merely a concomitant phenomenon, they give us a tangible evidence of cerebral function which should be of great help in neurophysiology, and is already of clinical importance in the localization of cerebral dysfunction.

HENRY WISE NEWMAN, M.D.

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PHYSIOLOGY

PROCEEDINGS OF
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Osmotic Pressure Studies on Blood Serum. I. Construction and Calibration of a Thermoelectric Vapor Pressure Apparatus. E. G. WITTING and C. G. GROSSCUP (Abington Memorial Hospital Laboratories, Abington, Pa.). In connection with certain studies on water and electrolytes being carried out in these laboratories it was desired to have a rapid, accurate method of measuring the colligative properties of solutions without employing freezing procedures. Construction of a modified Hill's apparatus is described and preliminary measurements given and discussed.

The apparatus consists of electrically opposed thermal junctions upon which distilled water and the sample solutions are placed. The measurements are made with the thermocouple chambers immersed in a tank of water maintained at a constant temperature by means of a toluene-mercury thermostat. Current output of the thermocouple is read on a high sensitivity Leeds and Northrup galvanometer (sensitivity, 0.0125 microvolts per millimeter under special conditions of operation, coil resistance 16 ohms, external damping resistance 10 ohms).

Electrical circuits are shown and described so that construction could be duplicated if desired.

Osmotic Pressure Studies on Blood Serum. II. Normal and Pathological Human Serum. CHARLES G. GROSSCUP, and JOHN EIMAN, (Abington Memorial Hospital Laboratories, Abington, Pa.). Forty samples of serum from 33 individuals have been analyzed for water, chloride, CO_2 capacity, total protein, urea nitrogen, non-protein nitrogen, glucose, total base, sodium, and equivalent osmotic pressure (EOP). The series includes 6 normals, preëclamptics, standardized diabetics, cases with renal involvement, a hypophyseal cyst and others with chemical imbalance due to various causes.

In each case, except those with elevated non-protein nitrogen, the observed EOP is less than the corresponding total base, despite the presence of significant amounts of glucose and urea in the serum. To account for this apparent discrepancy a careful estimation of the osmotic concentrations of the serum solutes was made for each case. For the

entire series the average ratio observed/calculated EOP is 0.938, with a standard error of the mean of ±0.005. Addition of urea and glucose to sera indicated that these substances exerted essentially their calculated osmotic effects. On the assumption that any errors of calculations must reside largely in the electrolyte fraction, an average osmotic coefficient for the salts was computed such that the observed and calculated EOP would agree. This value was found to be 0.86 (Standard error = ±0.01) in comparison to 0.93 for pure NaCl in water.

A study of the measured acid and base fractions for the 6 normal individuals shows an average total base of 160.3 and an average determined total acid of 159.3. This leaves little room for any substantial error in the base assigned to protein.

Regression equations relating EOP, total base, glucose and nonprotein nitrogen are developed. The coefficients of multiple correlations are high, 0.87 to 0.97.

Considering all factors we are inclined to believe that the thermoelectric vapor pressure method, in our hands at least, does not measure the total osmotic pressure of serum but only some (93 to 94%) of it. This fraction is quite constant and suitable correction may be made for it. The method thereby retains its usefulness and has proven satisfactory in the rapid construction of a blood picture for diagnostic and therapeutic measures.

Rhythmic Changes in Blood Flow Through Muscles. LAURENCE IRVING (Edward Martin Biological Laboratory, Swarthmore College, Swarthmore, Pa.). When the Hering-Traube-Mayer type of waves in arterial blood pressure appeared in anesthetized cats, corresponding rhythmic changes were observed in flow through muscle. Flow changes were determined in single muscles by an electrically heated resistance wire indicator operating on the principle of the hot wire anemometer. As blood pressure increased flow diminished in the single muscles. The changes in flow in one muscle were therefore representative of a major part of the peripheral circulation, and the vasoconstriction diminishing flow was the active basis of the change in pressure. Sympathectomy made flow changes in the muscle follow changes in blood pressure passively. The rhythmic changes in circulation were not rapidly altered by vagotomy and cutting the carotid sinus nerves. The rhythm could persist after curarization and artificial ventilation. The rhythmic change in flow, normally controlled over the sympathetic nerves, may be regarded as evidence of the nature of the central mechanism controlling the peripheral circulation. If the rhythmic activity represents a vasomotor center, its operation is quite stable during mechanical alteration of breathing by vagotomy, curarization and artificial ventilation, and frequent periods of apnea produced by inflation of the lungs. The "center" appears to be relatively independent of the control of breathing. Removal of chemoreceptors likewise did not greatly alter the rhythms. This type of peripheral vascular activity, with its possibility of differentiation, should be useful in characterizing the operation of the persistent control of vascular state which is the presumed function of the vasomotor center.

Measurements of the Uterine Contractions in Late Pregnancy With the Lorand Tocograph. D. P. MURPHY (Gynecean Hospital Institute, University of Pennsylvania). Five patients, all pregnant for the first time, were studied with a Lorand tocograph during the last 2 months of pregnancy. Observations were made on an average of 3 times a week. One hundred and six records, which represented approximately 120 hours of observation, gave 1377 uterine contraction waves for study. The wave pattern was similar in the same patient from day to day, but differed widely from patient to patient. There was a steady increase in the measurements of the various uterine motility characteristics as labor was approached, with an unusual increase during the week immediately preceding the onset of labor.

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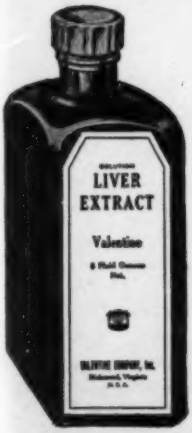

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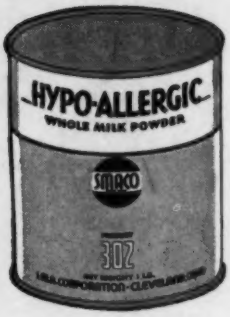

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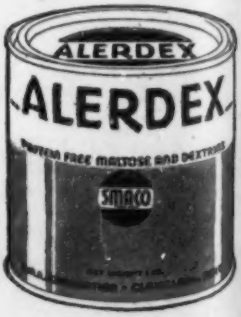

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